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Controversies in the Management of Gynecological Cancers

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Preface

Gynecological malignancies comprise a wide range of different tumors with various etiologies, risk factors, and treatment principles. Prevention, diagnosis and primary treatment, and the management of recurrence are complex issues; each type of tumor requires specialized knowledge at every phase of intervention. Disseminating expert knowledge and improving the treatment of these relatively uncommon diseases requires international networking and collaboration. In this book, we have taken a number of controversial areas in the diagnosis and management of gynecological cancers. Each chapter discusses a topic that continues to stimulate discussion within the gynecological cancer community. In some situations, clinical trials are needed to establish evidence-based answers to questions that have been present for many years. In other areas, where treatment practices vary and strongly held opinions prevail, there is considerable debate about the right way forward.

The concept of this book arose from discussions within the Gynecological Cancer Intergroup (GCIG), an international organization of 24 national trials organizations committed to work together to improve the outcome of women with gynecological cancers. Initially, the GCIG was a small group formed to conduct collaborative clinical trials. Its size has grown considerably since it was formalized 16 years ago and it now holds periodic meetings to produce, for example, a consensus for the management of ovarian cancer, and trial planning strategy meetings for ovarian, cervical, and endometrial cancers and rare gynecological malignancies. Translational aspects are emphasized.

We have selected as chapter topics for this book a number of clinical scenarios for which there are no definitive answers. Examples include new questions that have arisen from the rapid increase in knowledge we have seen from advances in understanding the biology of gynecological cancers, the effect on treatment decisions, and the opportunities that arise for developing new therapies. Other topics include those for which controversy about management continues, while we await a greater body of evidence to emerge about this best treatment. We have selected an international group of authors and have asked them to work together to produce a book dealing with the key controversies currently faced by doctors caring for women with gynecological cancers. Within each chapter, there are major subheadings posing questions on management, or arguing "pro" and "con" views that have not been resolved by an adequate evidence base, or for which evidence is conflicting. We have for each chapter either chosen authors with opposing views, or experts in the field, able to argue either side of the controversy.

The aim of this book is not to provide a comprehensive reference text, but rather to undertake a thorough discussion of current clinical topics relevant to everyday practice. Readers will be able to select topics to gain a greater understanding of the controversies that currently exist and be guided about the directions for future research in each of the areas discussed.

We would like to thank all the authors for the considerable time they gave and the effort they have made to contribute to this book. We would also like to acknowledge the staff at Springer who have supported us through this journey.

This book is dedicated to our patients who have taught us a great deal about the management of gynecological cancers, and to all those who have participated in clinical trials and studies to advance the knowledge and treatment of gynecological cancers.

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Controversies in the Treatment of Women with Early-Stage Epithelial Ovarian Cancer

1

Christina Fotopoulou, Ann Marie Swart, and Robert L. Coleman

Summary Points

- Surgery and chemotherapy play important roles in the treatment of women with epithelial ovarian cancer. In early disease, when there is the best chance of cure, optimizing treatment with both modalities without overtreatment can be a challenge.
- What initial surgery should be performed, both for those women who have a diagnosis of ovarian cancer prior to surgery and those whose cancer is diagnosed at or after surgery? In particular, what are the options for women who wish to preserve their childbearing potential?
- What clinical trial data can inform the need for and the choice of adjuvant chemotherapy regimen?

Introduction

Despite global efforts to optimize systemic and surgical management of epithelial ovarian cancer (EOC), it remains a disease that is primarily diagnosed at an advanced stage with extra ovarian and extra pelvic tumor involvement (FIGO III and IV) in over 70 % of the affected women [1, 2]. The prognosis of early-stage disease is significantly better than in the more common late-stage disease, with 5-year survival varying from 80 to 93 % (stage I/II) to <30 % (stage III/IV) [2–5]. Women diagnosed with stage I disease constitute a minor subgroup and are frequently identified serendipitously, being explored for a pelvic mass or for pelvic-related symptoms. These women do not generally represent a major surgical challenge in terms of multi-visceral resection techniques [6, 7]; however, accurately assessing stage is paramount to making informed decisions about appropriate adjuvant therapy. It is well described that occult disease is identified in 10–30 % of women with disease first thought to be confined to the ovary. For those who do have organ-confined disease and who are of childbearing age, consideration must be given to options of fertility-sparing surgery.

Informed choices for women with early EOC are limited by the paucity of randomized trials. Well-powered trials in this group of women are challenging due to the comparatively low incidence of early-stage disease [8] and the need for very long-term trials (>10-year follow-up) because of the relatively good prognosis, particularly when tumors are thoroughly staged.

Increasingly, these patients are excluded from participation in randomized clinical trials or relegated to a stratum where only hypothesis-generating assessments can be made. The irony in this clinical trial decision is that these patients frequently present with histologies (e.g., clear cell, endometrioid, low-grade serous) which are increasingly being identified with actionable molecular targets and, as such, may represent ideal patients to treat with novel targeted therapies [9]. When they are included in advanced disease trials, patients with early-stage disease [10–14] form small strata making evidence-based, specific recommendations for these women extremely

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difficult. To maximize information from randomized trials, extended follow-up, international collaboration, and meta-analyses are essential. The issue of when and how to treat early-stage OC is becoming increasingly important, with the identification of incident early-stage cases during prophylactic risk-reducing surgery in patients at high risk of developing OC (e.g., BRCA 1/2 carriers) and the potential for a further significant increase if cases of population screening trials (e.g., UKCTOCS [15]) are positive and demonstrate the ability to identify an increased proportion of patients with early-stage disease.

In this chapter, we address the most controversial issues regarding the treatment of early-stage EOC focusing on the therapeutic and prognostic implications of reoperation for staging after suboptimal initial surgery, the value and anatomic limits of systematic lymph node dissection at primary surgery, the role of minimally invasive surgical techniques, the type and duration of optimal adjuvant treatment, the value of targeted agents, the implementation of alternative chemotherapy regimens such as dose-dense delivery, optimal trial designs, individualized treatment approach, fertility-sparing surgical objectives, and hormone replacement and quality of life.

What Is the Role of Formal Staging Surgery for Women with Apparently Early EOC?

Since validated methods for early detection (e.g., preoperative imaging and biomarkers [CA125, HE4, OVA1]) have yet to be established, stage I disease is often identified incidentally [16]. Thus, many women initially undergo laparotomy or laparoscopy with the expectation of benign disease and may not therefore undergo adequate staging. National and international guidelines demand completion of adequate surgical staging in those cases where initial surgery was insufficient. In women for whom future fertility is important, the question of ovarian preservation complicates decisions regarding the extent of resection (cystectomy versus oophorectomy, unilateral versus bilateral resection) and the need for formal staging (risk of periovarian adhesions) [17, 18].

There are a number of arguments for the case for surgical staging:

1. Accurate surgical staging may result in unmasking of occult advanced disease (upstaging) which in turn has implications for defining optimal adjuvant treatment significantly influencing survival. Furthermore, a subgroup of patients may be identified where observation alone would suffice and the toxicity of any systemic chemotherapy avoided.

   Also, without accurate disease description, women may not be able to participate in clinical trials or benefit from future treatments with novel targeted therapeutics, tumor-specific vaccines, or immunotherapy regimens, which require accurate disease description to be available. Women with limited stage disease, arguably, may represent the ideal cohort for lasting tumor control in these programs and hence represent a cohort with the highest cure potential.
2. There is sufficient evidence that in early EOC existing conventional imaging modalities fail to accurately demonstrate peritoneal involvement, especially in the case of small volume disease. Although newer imaging modalities such as FDG-PET/CT and diffusion-weighted MRI (DW-MRI) offer an overall performance advance or an important adjuvant to conventional CT imaging, peritoneal deposits under 1 cm are frequently underappreciated by all imaging modalities [19]. Therefore, surgical assessment is still considered the most reliable method to accurately define disease distribution. The Gynecologic Oncology Group (GOG) has proscribed the surgical procedures required for complete staging in their EOC clinical trials (Table 1.1).

Table 1.1 GOG staging procedure for ovarian cancer [89]

GOG staging procedure for ovarian cancer
1. Vertical incision
2. Send peritoneal fluid. If none, send peritoneal washings
3. Inspect and palpate all peritoneal surfaces
4. Omentectomy
5. TAH-BSO
6. Resect gross disease within the abdominal cavity
7. In absence of disease beyond the pelvis, peritoneal biopsies
8. Pelvic and para-aortic nodes for:
Stage IIIB disease (microscopic disease in omentum 2 cm)
Not required for stage IIIC or IV disease, unless only disease is a palpable node

Table 1.2 Rates of upstaged women after accurate surgical staging in apparently early EOC

Structure affected by tumor in apparently early ovarian cancer after adequate staging	Rate of women [88] (%)
Cytology	20
Omentum	6
Diaphragmatic peritoneum	15
Random peritoneal biopsies	13
Para-aortic lymph nodes	14
Pelvic lymph nodes	8

Depending on the histological grade and subtype, up to 30 % of the women with apparently early EOC will be upstaged after comprehensive surgical staging [18, 20]. Table 1.2 presents the rates of upstaged women after accurate surgical staging in women with apparently early EOC.

In a more recent retrospective evaluation of 86 women with EOC grossly confined to the ovary in whom complete surgical staging was performed, 29 % were upstaged, 6 % had metastatic disease in uterus and/or fallopian tubes, 6 %

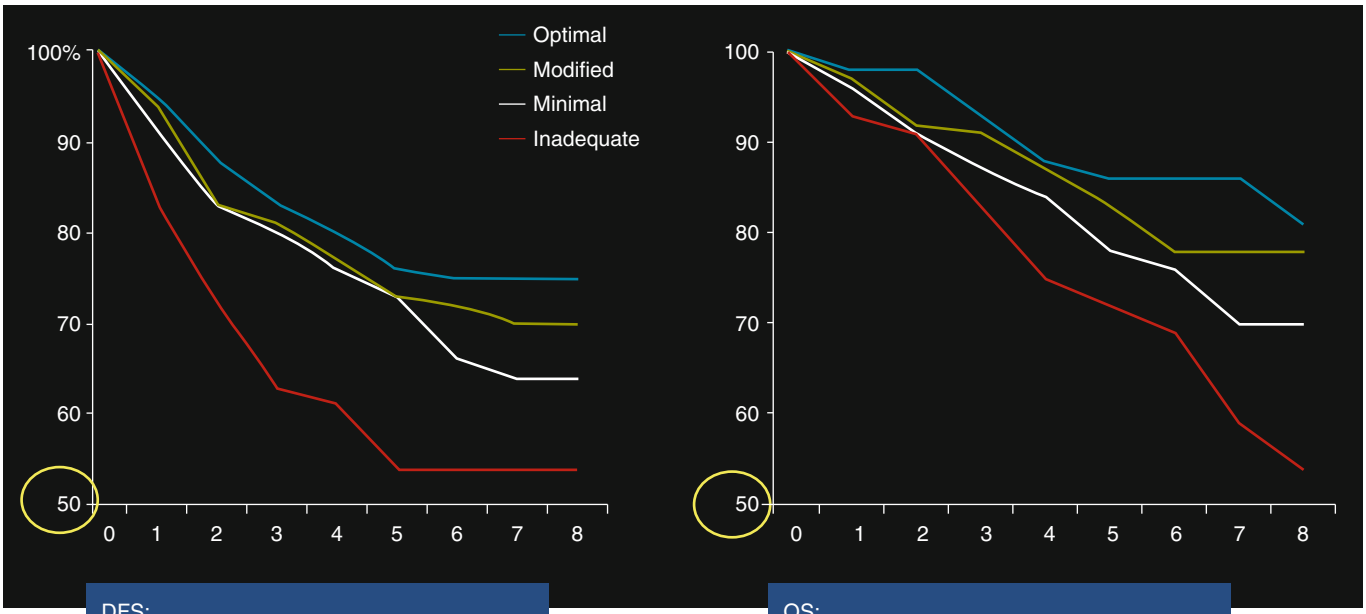

Fig. 1.1 DFS and OS according to quality of staging

in lymph nodes, and 17 % in peritoneal, omental, or adhesion biopsies [20]. In a larger analysis including 122 women of mainly stage IA (33 %) and IC (41 %) disease, a total of 19 women had positive peritoneal biopsies (16 %) at surgical staging. Even though only six (5 %) of those were from normal-appearing tissue, comprehensive staging resulted in upstaging of 4 % of all women by the random peritoneal biopsies alone. Five (4 %) women had microscopic metastases to the omentum, four (3 %) of whom were upstaged by this finding alone [21]. The authors concluded that although the rate of microscopic metastases to peritoneal tissue is low, random peritoneal biopsies might still be indicated in early-stage disease, especially considering the low morbidity of the procedure and the rapid regeneration of the peritoneum.

Unfortunately, trials conducted in early-stage disease are bereft of standardized surgical staging procedures leading to difficulty in interpretation of the value of the procedure itself. A subanalysis of EORTC Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial evaluated the staging characteristics of the incompletely staged cancers as well as factors leading to this outcome. Despite being an eligibility criterion, complete surgical staging was performed in only a minority of participants (34 %) [18]. The authors identified lack of surgical skills accounted for the majority of the deviations. This was followed by insufficient knowledge of the tumor behavior and routes of spread of ovarian cancer, especially in low-volume centers. Figure 1.1 presents the ACTION data regarding the significant impact of surgical quality, as measured on the completeness of staging in early EOC, on disease-free survival (DFS) and OS.

Should Patients with Inadequately Staged Early Ovarian Cancer Undergo a Second Operation?

The arguments against reoperation are:

1. Patients with organ-confined disease (i.e., IA or IB) do not need to undergo unnecessary second surgery with all associated short- and long-term morbidity if at first surgery all peritoneal surfaces appear unaffected by tumor and there are no abnormalities on postoperative imaging. Postoperative chemotherapy will be administered under these circumstances, and thus, incomplete surgical staging can be sufficiently compensated.
2. No prospectively randomized trials exist to establish the prognostic and/or therapeutic value of surgical staging in early EOC. Moreover, there is no evidence-based therapeutic

impact of removing microscopic disease in women already considered with "optimal" postoperative tumor residuum by advanced disease standards (so called R0 resection) [9, 22–25]. A retrospective analysis by Dizon et al. [17] of 88 women with stage I–II disease failed to identify any survival advantage of completion of surgical staging in women who underwent chemotherapy with 6 cycles of carboplatin and paclitaxel. With a median follow-up of 50 and 59.5 months, respectively, for staged versus nonstaged women, 5-year PFS was 85 % versus 80 % (p=0.54). Accordingly, no benefit in OS was identified with 5-year OS-rates of 85 % versus 88 %, respectively (p = 0.688). Another retrospective analysis by Le et al. [26] reviewed the impact of comprehensive surgical staging in a group of 138 women with tumor confined to the ovary. In the group of women given adjuvant platinum-based chemotherapy at a median follow-up of 58 months, 11 out of 34 (32 %) staged women relapsed compared to 8 out of 19 (42 %) unstaged women, a difference which was not statistically significant. These data raise the hypothesis that planned adjuvant chemotherapy can normalize the therapeutic difference, if it exists, between unstaged and staged women, obviating the unnecessary morbidity of a second surgery.

Some practitioners have advocated that random biopsies or omentectomy may be a surrogate for staging in cases where expert surgical help is unavailable. However, the value of random sampling of this nature is even more inconclusive. Retrospective studies suggest that random peritoneal biopsies add only little diagnostic value beyond careful inspection of the peritoneal surfaces [27]. A retrospective evaluation of 211 women with apparent early EOC revealed that only 9 women were upstaged based on pathology, hence indicating a high negative predictive value of thorough exploration and lymphadenectomy. Only one patient (1/118, 0.8 %) was upstaged from stage I disease to stage II disease based on random biopsy of pelvic peritoneum, since all other stage II women had visible disease. Interestingly, no women were upstaged from stage I disease to stage III disease due to random biopsies or microscopic omental disease. Eight women (3.8 %) were upstaged from stage II to stage III disease based on random biopsies of upper abdominal peritoneum or the omentum. Interestingly, the authors report that their treatment recommendations for adjuvant therapy were unaffected by the findings from random biopsies [27].

In summary, the available data suggest that there is merit to formal surgical staging in women where disease may be observed or in cases where such information is required for participation in a clinical trial. Women with high-risk features are prime candidates for adjuvant therapy; those without gross disease likely gain little specifically from formal staging; however, those with suspected residual disease should be explored for cytoreduction. Fertility-sparing procedures (retention of the uterus, fallopial tubes, and contralateral ovary in case of unilateral disease) appear safe, although removal of the ovaries at the completion of childbearing wish may be recommended.

Table 1.3 Rate of women with apparently early EOC with positive pelvic and/or para-aortic lymph nodes after systematic lymph node dissection

Author	Number of patients in study	%
Benedetti-Panici [28]	35	14
Petru [29]	40	23
Onda [30]	33	21
Baiocchi [31]	242	13
Suzuki [32]	47	11
Nomura [33]	79	13
Harter [43]	70	11

Should Complete Bilateral Pelvic and Para-aortic Lymph Node Dissection (LND) Be Part of Routine Staging?

The standard approach to surgical removal of retroperitoneal nodes in EOC remains controversial. Even when the tumor is seemingly limited to the ovaries, spread to retroperitoneal nodes is not uncommon [28–33]. For that reason surgical staging includes the inspection and dissection of pelvic and para-aortic lymph nodes. What is not defined so far is how extensive the LND needs to be and if a sampling is sufficient compared to systematic dissection [34].

The Arguments for Systematic LND

The value of systematic LND lies in the accurate staging of the apparently early EOC by unmasking all occult IIIC stage disease; an upstaging that would have significant impact on decision-making process regarding adjuvant therapy. This is highlighted by the approval of antiangiogenesis therapy for advanced-stage (>stage IIIB) disease in many countries [35]. As is the case for formal peritoneal assessment of apparent early-stage women, systematic tissue sampling, in this case, lymph nodes, will identify occult disease in a proportion of women with nonclinical disease. The rate of pelvic and para-aortic node involvement is 8–15 % and 5–24 %, respectively (Table 1.3) [34, 36, 37]. In the prospective randomized trial by Maggioni et al. significantly more women in the systematic LND group had positive nodes at histologic examination than women in the lymphatic sampling arm (9 vs. 22 %, p=0.007). In this study, an adequate LND was defined as removal of 20 or more nodes in a bilateral pelvic retroperitoneal dissection and 15 or more nodes from the para-aortic chains. In addition, significantly more women undergoing sampling were administered postoperative systemic chemotherapy in the absence of formal surgical staging information

(66 % vs. 51 %, $p=0.03$). Further, these occult stage IIIC women would have been eligible for participation in advanced-stage clinical trials. And finally, women with stage IIIC disease determined solely on the basis of histologically positive retroperitoneal adenopathy appear to have a better prognosis over those stage IIIC women identified by gross intraperitoneal spread [38]. A criticism for formal surgical staging is the increased risk of operative and perioperative morbidity. In this trial, rates of transfusion and the hospital stay were increased in the systematic LND arm; however, neither the number of intraoperative nor perioperative/late complications were statistically different between the two groups (8 cases vs. 4 and 8 cases vs. 16 in the control and lymphadenectomy arm, respectively). Regarding late morbidity, most of the difference was due to formation of lymphocysts and lymphedema, which occurred in eight cases in the lymphadenectomy group versus none in the control arm. Adhesive small bowel obstruction occurred in one patient after lymph nodes sampling only and in two women after lymphadenectomy. There were no surgery-related deaths in either arm of the trial. The authors conclude that although their study was underpowered to detect an effect of systematic LND on PFS or OS, the trends in the point estimates for these hazard ratios favored the procedure particularly in light of the accuracy of diagnosis precluding some women from receiving unnecessary adjuvant therapy.

The Arguments Against Systematic LND

There is no evidenced-based benefit of systematic LND in apparently early EOC. The only randomized clinical trial of women with EOC macroscopically confined to the pelvis that compared systematic LND and lymph nodes sampling failed to identify any significant impact on PFS or on OS [34]. Considering the higher morbidity and effort of systematic LND compared to sampling alone, LN sampling should suffice for complete staging in early disease.

The only randomized trial assessing systematic LND in this setting aimed to evaluate surgical and clinical outcomes [34]. As presented above, the authors failed to identify any significant benefit of systematic LND regarding PFS or OS. At a median follow-up of 87.8 months, the adjusted risks for progression ([HR]=0.72, 95 % CI=0.46–1.21, $p=0.16$) and death (HR=0.85, 95 % CI=0.49–1.47, $p=0.56$) were lower, but not statistically significant, in the systematic LND. Five-year PFS rates were also equivalent between the two arms: 71.3 versus 78.3 % (difference=7.0 %, 95 % CI: –3.4 to 14.3 %) and 5-year OS was 81.3 versus 84.2 % (difference=2.9 %, 95 % CI=7.0–9.2 %), respectively, for sampling versus systematic LND. At the same time, surgical morbidity was significantly greater in the systematic LND arm, referring to significantly longer operating times by a median of 90 min ($p<0.001$), doubling of intraoperative blood loss (300 vs. 600 ml; $p<0.001$) with accordingly higher rates of transfusions needed (21.8 vs. 35.5 %; $p=0.012$) and significantly longer hospital stay times: 1 day in median longer ($p=0.003$).

Considering the described short- and long-term morbidity of systematic LND, such as potential vessel injury, thromboembolic risk, formation of lymphocysts and lymphedema, and adhesive small bowel obstruction in the absence of survival benefit, there is currently no indication for extensive systematic LND in apparent early EOC. This is consistent with the current trends throughout surgical oncology specialties, where extensive LND have been replaced with lesser morbid diagnostic evaluations, such as lymphatic sampling and sentinel lymph node identification.

In summary much of the support for systematic LN comes from retrospective and prospective nonrandomized studies of women with limited-appearing disease (no intraperitoneal disease) who had formal lymphatic dissection identifying metastatic disease in a small proportion [39]. The impact of this identification of occult disease is countered by the relationship of nodal spread and other high-risk features, such as high-grade, tumor rupture/surface involvement or positive cytology. These cases most often receive adjuvant chemotherapy, which could be anticipated to level the survival outcomes between LND and non-LND women. Under these assumptions, the therapeutic value of LND would have to be carried by the few low-risk women who did not receive adjuvant therapy and were not identified by the surgical procedure. Even the aforementioned randomized study could not completely evaluate the procedure fairly because adjuvant therapy was not prespecified and likely could be unethical given the mortality of recurrent disease. Our recommendation is to extend the surgical staging procedure to the retroperitoneum with the same intent as other potential metastatic sites. Until the value of a complete LND is shown, it should be avoided in order to spare the long-term morbidity from surgery that may be experienced in these “curable” women. A possible exception may be mucinous early EOC. Increasing evidence shows that the rate of positive LN in stage IA mucinous cancer is extremely low (near 0 %), reducing the value of any LND in this subgroup of women [40–42].

In Apparently Early Unilateral Disease, Is Unilateral Pelvic LND Sufficient for Adequate Staging?

This clinical issue is less a matter of “controversy” as it is an intraoperative consideration for women with stage IA disease or in cases where fertility preservation is being considered. Retrospective evidence reveals that 3.5–11 % of the women with unilateral disease will have contralateral pelvic lymph node metastases despite negative ipsilateral nodes

[28–45]. A recent large systematic review regarding lymph node metastases in early stage I and II EOC included 14 studies and showed that the mean incidence of lymph node metastases in clinical stages I–II EOC was 14.2 % (range 6.1–29.6 %), of which 7.1 % had isolated disease in the para-aortic region, 2.9 % isolated to the pelvic region, and 4.3 % in both lymphatic basins. According to histological subtype, the highest incidence of lymph node metastases was found in the serous subtype (23.3 %); the lowest was in the mucinous subtype (2.6 %). In unilateral tumors, pelvic lymph node metastases were found in 9.7 % on both sides, 8.3 % only at the ipsilateral side, and in 3.5 % only at the contralateral side [41]. Other analyses describe even higher rates of solely contralateral LN metastases of 11 % [42].

Summary

The low rate of contralateral metastases in the setting of negative ipsilateral nodes in women with stage IA disease lowers one's enthusiasm for "routinely" performing the procedure. However, accurate information at the time of surgery is largely unknown, and with bilateral rates being as high as 8 % in women with stage IA disease, exploration is indicated. Women with fertility preservation goals should be counseled to the risk-benefit trade-off of not performing a pelvic node dissection in the hopes of reducing postoperative tubal/ovarian adhesions. There may be an opportunity to assess lymphatic mapping in these cases as newer intraoperative imaging techniques, such as near-infrared fluorescence lymphatic tracers become available [46].

Is Fertility-Sparing Surgery a Viable Option for Women with Early-Stage Epithelial Ovarian Cancer?

Organ and fertility-preserving surgery in a highly aggressive disease such as EOC constitutes a therapeutic dilemma for treating physicians and affected patients. The desire for the best clinical outcome with respect to cancer cure may be counterbalanced by a desire for organ sparing to maximize the chance of future childbearing. Furthermore, the hormonal milieu of pregnancy and puerperium may increase risk of EOC recurrence.

Review of the available clinical data suggests that fertility-sparing surgery (FSS) in early-stage EOC is a reasonable option for women younger than 40 years who wish to preserve their childbearing potential. However, careful consideration of histologic subtypes is warranted. The optimal indication appears to be stage IA G1/G2 disease. Less clear is stage IC disease. In IC disease the value of histological subtype has to be additionally considered: e.g., non-clear cell, and the way IC was determined (ovarian surface involvement vs. iatrogenic rupture vs. spontaneous rupture). Iatrogenic rupture has been associated with less favorable outcomes after FSS in terms of reduced conception potential and less favorable overall prognosis [47].

Satoh et al. systematically studied selection criteria for FSS in 211 stage I EOC (stage IA, $n=126$, stage IC, $n=85$) women based on clinical outcomes [48]. The majority of the women underwent unilateral salpingo-oophorectomy ($N=205$), with 142 (69 %) having additional "staging" procedures (e.g., omentectomy, lymph nodes, and biopsy of the contralateral ovary); 6 women had cystectomy. At a median follow-up of 78 months, 18 (8.5 %) of women recurred with 5 (28 %) recurring in the retained ovary; all 5 of these women were salvaged with surgery. Of those recurring outside the ovary, 3 were without evidence of disease, 5 were alive with disease, and 5 had died of disease. Recurrence was linked to stage IC disease, grade 3 histology, and unfavorable cell types (in this study, clear cell).

In the analysis of recurrent disease, nonlocal recurrence was associated with a significantly higher mortality rate compared to recurrence in a retained ovary exclusively. Thus, based on these observations and patterns of recurrence, the authors recommended that FSS is safe in women with stage IA, grade 1 or 2, and favorable histology, with or without adjuvant chemotherapy. In addition, women with stage IA clear cell or stage IC with unilateral ovarian involvement and favorable histology would be amenable to FSS as long as they underwent complete surgical staging and adjuvant platinum-based chemotherapy. FSS was not recommended in stage IA, G3 disease or stage IC, and clear cell or G3 histology as these women represented the highest risk for recurrence and nonlocalized recurrence [48]. The fertility rate in those attempting conception after treatment was 53 %.

While this trial represents the largest patient cohort examined, the results are consistent with others in the literature [49–55]. In these studies, the mean relapse rates are approximately 10 %, although many also include women with stage IC disease. Nevertheless, when accurately examining the characteristics of the women who suffered from relapse, they belonged mainly to the subgroup with IC and/or G3 tumors. Interestingly, many studies failed to demonstrate differential outcomes based on the way stage IC was allocated. That is similar outcomes were seen among those with iatrogenic rupture, those with positive cytology, and those with ovarian surface involvement. Kajiyama et al. [54] assessed survival after FSS in women with either iatrogenic rupture versus surface involvement/positive cytology. They concluded that while PFS and OS were significantly worse for women with stage IC (surface involvement/positive cytology) compared to those with stage IA after FSS, there was no difference in survival in women with stage IA disease compared with those with stage IC disease based on iatrogenic rupture. In the study of Zanetta et al. none of the women undergoing bilateral oophorectomy had microscopic foci of cancer in the normal-looking contralateral ovary suggesting contralateral biopsy to be of little value in these circumstances [49]. In two

recent studies, the feasibility of fertility-sparing surgery was assessed in women with clear cell or mucinous carcinoma of the ovary, two histological types which have been associated in various reports with a rather less favorable prognosis [48, 54]. In both analyses, the authors concluded that FSS in presence of these two histological subtypes was not necessarily associated with a poorer prognosis compared to radical surgery and hence is feasible. The incongruence may be attributed to the negative impact of unfavorable histology on survival in advanced-stage (stage III/IV) disease [9, 56].

These data highlight the difficulty in profiling women at greatest risk for relapse following FSS, even women with stage IA disease as many of the existing studies include women with varying degrees of accurate surgical staging [48, 57]. Overall, reported disease-specific death rates are ranging between 2 and 15 %.

Fertility Success: Results

Successful fecundity rates after FSS in all women who present with early EOC is about 30 %; however, this rate rises to more than 66 % in various series if the denominator includes only those who actively tried to conceive. These are close to fecundity rates for noncancer women. Also, where reported, only a minority of women ultimately conceiving after FSS required assisted reproductive techniques [47]. The incidence of spontaneous abortions ranges between 11 and 33 % and is also consistent with the general age-matched population. These data might be expected as the rates of normal menstrual function following FSS is close to 97 % [48]. In this series, 6 (5.0 %) of the 121 women who received platinum-based chemotherapy presented with persistent secondary amenorrhea up to 224 months after completion of 4–6 cycles of adjuvant treatment. Five (9.1 %) of the 55 women who successfully conceived did so with assisted fertility treatments. Interestingly, only a minority of these women (9.4 %) underwent completion surgery after childbearing, consisting of hysterectomy and contralateral salpingo-oophorectomy. Where reported, none of the women who successfully conceived and gave birth presented any relevant, cancer-related clinical problems during the perinatal period. Also no higher rates of congenital malformations or abnormal fetal outcomes have been reported in the current literature [47, 48, 58].

Women considering FSS in EOC should be thoroughly counseled to the risks and benefits to a conservative approach. Since new options (e.g., ovarian cortex cryopreservation, autologous transplantation) are becoming available to women considering future fertility preservation, we recommend counseling by fertility experts of the affected women with careful balancing of the risks and benefits. The treating gynecologic oncologist should be fully aware of the need to provide care for young women with malignant disease as well as taking account of her need to retain fertility by considering fertility-sparing alternatives when allowed so by tumor stage and histologic differentiation.

Future Directions: Fertility-Sparing Surgery

All women after FSS in early EOC should be systematically and prospectively collected in a central database with assessment of all factors regarding both oncologic and reproductive outcomes including hormonal stimulation treatments assisted reproductive technologies and years of attempting to conceive.

What Is the Optimal Adjuvant Treatment of Early EOC?

Which women to treat, the choice of the optimal adjuvant chemotherapy regimen and the duration of treatment in early-stage OC are subjects of continuing debate with no clear international consensus on two main issues. Firstly, is adjuvant therapy necessary in all patients with early EOC and secondly if adjuvant therapy is needed, what regimen and how much therapy is recommended? These questions are critical in this group of women that includes those with highest chance of being cured of their disease but also of being affected by longer-term side effects of surgical and chemotherapy treatments. Table 1.4 presents a summary of adjuvant trials in early-stage ovarian cancer, with observation as a control arm. There are a

Table 1.4 Early-stage ovarian cancer trials of platinum-based adjuvant therapy versus observation

Trial	*N*	Adjuvant treatment arm	Median follow-up (months)	Endpoint	HR adjuvant chemotherapy versus observation (95 % CI)	*p* value
Bolis et al. [81]	83	Cisplatin	71	RFS	0.48 (0.24–1.14)	0.095
				OS	1.15 (0.44–2.98)	0.773
Trope et al. [66]	162	Carboplatin	46	RFS	0.98 (0.52–1.83)	0.90
				OS	0.94 (0.37–2.36)	0.90
ACTION [22]	448	Platinum	59	RFS	0.63 (0.43–0.92)	0.02
				OS	0.69 (0.44–1.08)	0.104
ICON1 [59]	477	Platinum	51	RFS	0.65 (0.46–0.91)	0.01
				OS	0.66 (0.45–0.97)	0.03

number of challenges in interpreting the results of these trials. Firstly, the majority of the trials were too small to provide meaningful conclusions. Secondly, in order to recruit sufficient patients, the entry criteria were a broad range of early-stage (I and II) patients, for example, the ACTION and ICON1 trials included women with stage IA/IB, grade 2/3, stage IC/IIA, all grades, and clear cell histology. By modern standards, it is not helpful to have such a wide range of early-stage patients included.

The Case for Adjuvant Treatment

The two largest trials (ICON1 and ACTION) were set up in the 1990s to address the uncertain benefit of immediate adjuvant chemotherapy in early-stage disease, in terms of recurrence-free survival (RFS) and overall survival (OS) [22, 59]. The primary analysis of ICON1 on its own, with a median follow-up of 4 years, demonstrated a significant improvement in both RFS (hazard ratio (HR) = 0.65, 95 % CI = 0.46–0.91, $p = 0.01$) and OS (HR = 0.66, 95 % CI = 0.45–0.97, $p = 0.03$) in favor of immediate adjuvant chemotherapy [59]. Very similar findings were reported in the ACTION trial [22]. A preplanned combined analysis which included 925 women (477 from ICON1 and 448 from ACTION) randomized to platinum-based chemotherapy or observation was pooled for analysis [60]. At a median follow-up of 5 years, an 8 % OS benefit (82 vs. 74 %, hazard ratio = 0.67, 95 % CI 0.50–0.90, $p = 0.008$) and an 11 % recurrence-free survival benefit (76 vs. 65 %, hazard ratio = 0.64, 95 % CI 0.50–0.72, $p = 0.001$) were observed, favoring adjuvant chemotherapy. The magnitude of chemotherapy benefit was maintained in the performed subgroup analysis, even among women with stage IA disease. The sizes of these two trials were a major factor in a meta-analysis on the topic coming to the same conclusion [61].

Ten-year follow-up results of ICON1 and updated results from the ACTION trial are now available and provide further evidence to inform the debate. The updated median follow-up in ICON1 is 10 years with a further 32 women who relapsed (7 after 5 years), giving a total of 165 (35 %) women who have developed disease recurrence or died (71 immediate adjuvant chemotherapy, 94 no immediate adjuvant chemotherapy) [62]. Comparison of Kaplan-Meier curves for recurrence-free survival gives an estimated hazard ratio (HR) of 0.69 (95 % CI = 0.51–0.94, $p = 0.02$) (Fig. 1.2a). This translates into a 10 % RFS improvement from immediate adjuvant chemotherapy at 10 years, from 60 to 70 %. The absolute difference of RFS and 95 % confidence interval (CI) of the difference between immediate adjuvant therapy and no immediate adjuvant therapy over time is displayed in Fig. 1.2c.

A further 48 women died, giving 151 (32 %) deaths in total (66 immediate adjuvant chemotherapy, 85 no immediate adjuvant chemotherapy), of which 72 % were attributable to OC. Comparison of Kaplan-Meier curves (Fig. 1.2b) gave an estimated HR = 0.71 (95 % CI = 0.52–0.98, $p = 0.04$) in favor of immediate adjuvant chemotherapy, translating into a 9 % OS improvement at 10 years, from 64 to 73 %. The absolute difference of OS from immediate adjuvant therapy over no immediate adjuvant therapy over time is displayed in Fig. 1.2d.

The effect of immediate adjuvant chemotherapy in stage I patients ($n = 428$) by recurrence risk was explored using previously published risk stratifications [10] (Table 1.5, Fig. 1.2e for RFS and Fig. 1.2f for OS). The benefit of immediate adjuvant chemotherapy appears greatest in women with high-risk stage I disease. For RFS the HR = 0.48 (95 % CI = 0.31–0.73, $p < 0.001$) equates to an improvement at 10 years of 23 % (95 % CI = 11–33 %) from 45 to 68 %. For OS in these women, the HR = 0.52 (95 % CI = 0.33–0.81, $p = 0{\cdot}004$) translates into an 18 % (95 % CI = 7–27 %) improvement at 10 years, from 56 to 74 %. In the low-/intermediate-risk groups, for RFS, the HR = 0.92 (95 % CI = 0.52–1.64, $p = 0.78$) equates with a 2 % (95 % CI = −13 to 12 %) improvement at 10 years from 73 to 75 %; for OS the HR = 0.91 (95 % CI = 0.49–1.69, $p = 0.77$) gives an improvement at 10 years of 2 % (95 % CI = −12 to 11 %) from 78 to 80 %. The tests for interaction for RFS ($p = 0.075$) and OS ($p = 0.15$) are suggestive of a different size of effect between the high-risk and low-/intermediate-risk groups, but these tests have low power and the trial was not powered for testing interaction.

Long-term follow-up data from ICON1 therefore confirmed the long-term PFS and OS benefit from adjuvant platinum-based chemotherapy in women with early-stage OC. Results were consistent with previous trials and meta-analyses [22, 59–61]. The magnitude of benefit appeared greatest in women with high-risk early-stage disease, which indicates that chemotherapy should be standard of care in these patients. A small benefit in women with lower-risk early-stage disease could not be excluded, and the recommendation was that chemotherapy should be discussed, considering individual patient and disease characteristics including cyst rupture, age, and histological subtype [63–65]. Additional prognostic biomarkers have been reported which might enable selection of high-risk patients, including DNA ploidy [66–68], CA125 [25, 69], and HE4 [70], but data are conflicting and currently none are routinely used clinically to tailor treatments.

ICON1 was a pragmatic trial aligned with routine clinical practice at the time, designed to include patients in whom the indication for chemotherapy was uncertain, and without mandating specific disease staging. Despite this ICON1 remains the largest trial ever performed in early OC, and it is unlikely that trials in this setting without a major change in treatment modality (such as immunotherapy) and of this size will be repeated. The long-term follow-up of ICON 1 provides important confirmatory results that aid decision-making by clinicians treating women with early-stage OC. The updated results of the EORTC ACTION trial concentrate on a retrospective subgroup analysis investigating the effect of immediate

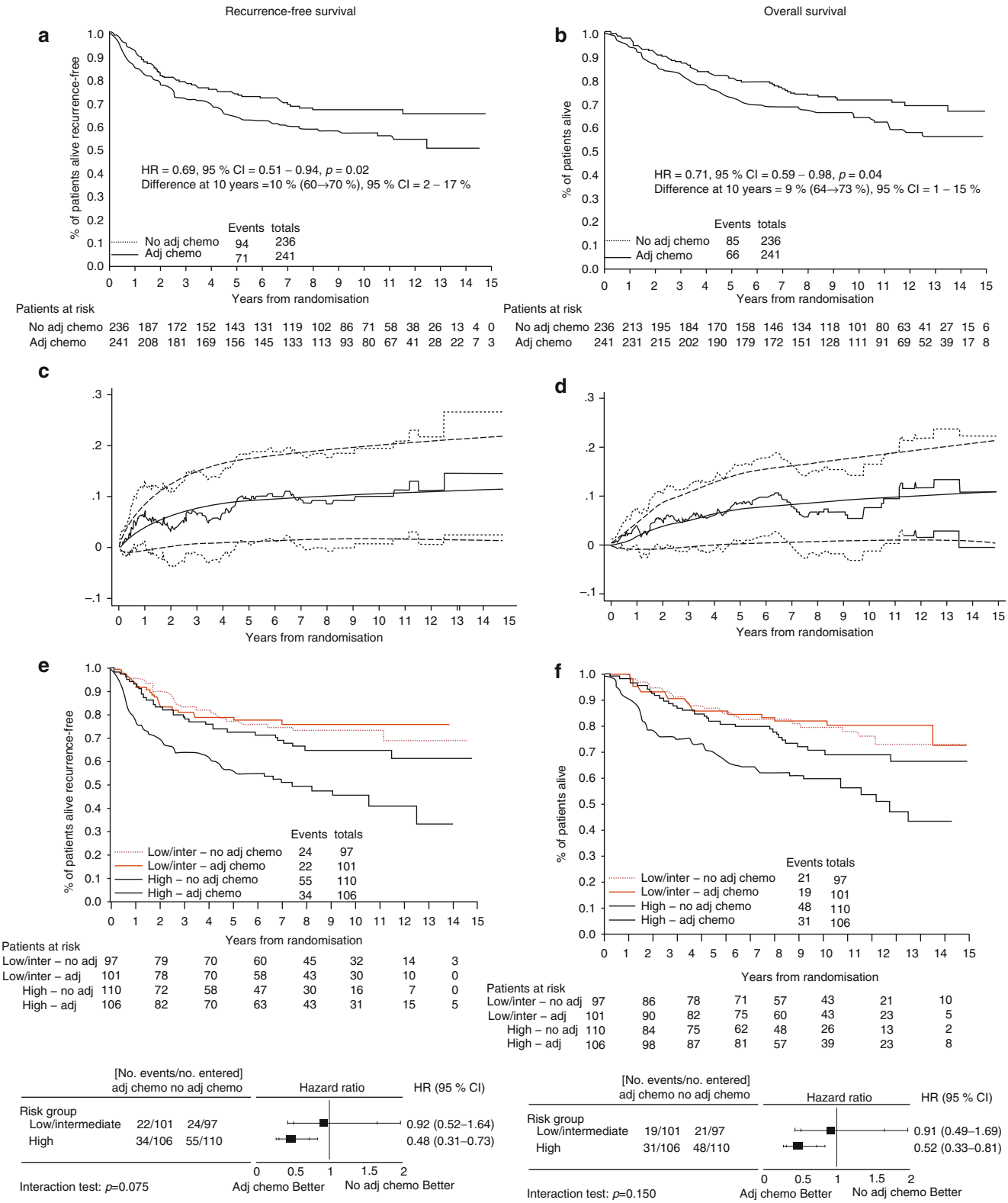

Fig. 1.2 Updated ICON1 results with median follow-up 10 years [62]. (**a**) Recurrence-free survival by treatment arms, (**b**) overall survival by treatment arms, (**c**) difference of recurrence-free survival (95 % CI) of immediate adjuvant therapy over no immediate adjuvant therapy over time, (**d**) difference of overall survival (95 % CI) of immediate adjuvant therapy over on immediate adjuvant therapy over time, (**e**) recurrence-free survival by treatment arms and risk groups, and (**f**) overall survival by treatment arms and risk groups

Table 1.5 Classification of stage I patients by risk of recurrence [10]

	Grade 1	Grade 2	Grade 3
Stage IA	13 %	20 %	10 %
Stage IB	3 %	4 %	4 %
Stage IC	15 %	17 %	12 %
Figures represent the proportion of patients in ICON1 (2 % unknown)			
Low risk (13 %)			
Intermediate risk (38 %)			
High risk (47 %)			

adjuvant chemotherapy in patients optimally surgically staged and those non-optimally surgically staged. Benefit of immediate chemotherapy was only demonstrated in non-optimally surgically staged patients; however, the subgroup of optimally surgically staged patients was small ($n=151$) [71]. Exploratory analyses by high- and low-risk patients were not possible in the ACTION trial as patients with lower-risk disease (grade 1 stage IA/IB) were excluded. One body of opinion is that, given the initial and long-term follow-up results of ICON1, the EORTC ACTION subgroup analyses do not provide sufficient evidence to exclude the benefit of adjuvant chemotherapy in the optimally staged cohort and that, if optimal staging can only be delivered in one-third of women even in a clinical trial setting, there is a strong argument to support treatment for a wide range of women with early ovarian cancer. However, even those who support the use of adjuvant treatment in selected low-risk patients recognize the caveat that this may result in overtreatment in unselected cases. Continued work evaluating key prognostic factors governing recurrence is necessary to better individualize treatment recommendations.

In conclusion, supporters of adjuvant treatment argue that the benefit of adjuvant postoperative chemotherapy for early-stage OC is confirmed with long-term follow-up of ICON1 and that the magnitude of benefit is greatest in patients with features that place them at a higher risk of recurrence.

The Case Against Adjuvant Treatment

While most clinicians and published guidelines recommend against routine adjuvant therapy in women with optimally staged IA grade 1 disease, all other scenarios raise questions that are difficult to answer from the available literature. A major criticism in the evidence to date is due to lack of quality control for surgical staging and the impact on generalizability of trial results which include a high proportion of patients for whom formal staging is unknown and who therefore might have had unrecognized advanced disease. As discussed earlier, only about one-third of the ACTION/ICON-1 cohort was optimally surgically staged. In a subgroup analysis of this cohort, the impact of adjuvant therapy was lost. Indeed, a meta-analysis of adequately staged, stage I women demonstrated no benefit from receiving additional chemotherapy (HR: 0.91, 95 % CI: 0.51–1.61) [64]. It is not known whether new biomarkers such as DNA ploidy or genomic biomarkers may help to bring better precision to the question of adjuvant treatment. Nevertheless, stage I women with high risk for recurrence (stage IC, clear cell, and grade 3 histology) are frequently recommended adjuvant therapy.

Summary

Adjuvant treatment for low-risk women remains controversial. Some may conclude that adjuvant chemotherapy is best reserved for women where accurate staging information is not available or in whom high-risk factors for recurrence are present, such as grade 3, clear cell histology, stage IC, and stage II disease. Women with grade 2 disease are more challenging as they have been both included and excluded from adjuvant trials.

What Is the Optimal Chemotherapy Regimen and Duration of Therapy?

When immediate adjuvant chemotherapy is used in early-stage OC, the choice of optimal chemotherapeutic regimen and duration of treatment also remains unclear. Some of the discrepancy is related to the adjuvant trials where physician discretion was allowed for type of chemotherapy and a range of 4–6 cycles. Single-agent carboplatin was the chemotherapy most frequently used in ICON1 and ACTION (87 % of patients in ICON1 and 57 % of patients in the combined ICON1/ACTION analysis) [60]. There were no treatment-related deaths in ICON1, but cytotoxic chemotherapy can have potentially serious and/or long-term complications [72], which are increased when taxanes are added to platinum-based therapy. In clinical practice, both carboplatin and carboplatin/paclitaxel are utilized in this setting, although there is no clear evidence base to support the use of combination therapy.

There are no prospective randomized clinical trials directly comparing the use of carboplatin and carboplatin/paclitaxel in this setting; however, data were available from stage I patients enrolled into the ICON3 trial, which compared the addition of paclitaxel to platinum-based adjuvant chemotherapy in patients with OC [73]. In ICON3, there were 120 (6 % of total) stage I patients randomized with a ratio of 1:2 to either carboplatin/paclitaxel ($n=44$) or single-agent carboplatin ($n=76$). After 51 months of median follow-up, 44 women have relapsed (13 carboplatin/paclitaxel, 31 carboplatin), and comparison of Kaplan-Meier curves shows a trend towards improved progression-free survival in favor of carboplatin/paclitaxel (HR = 0.71, 95 % CI = 0.39–1.32, $p=0.28$)

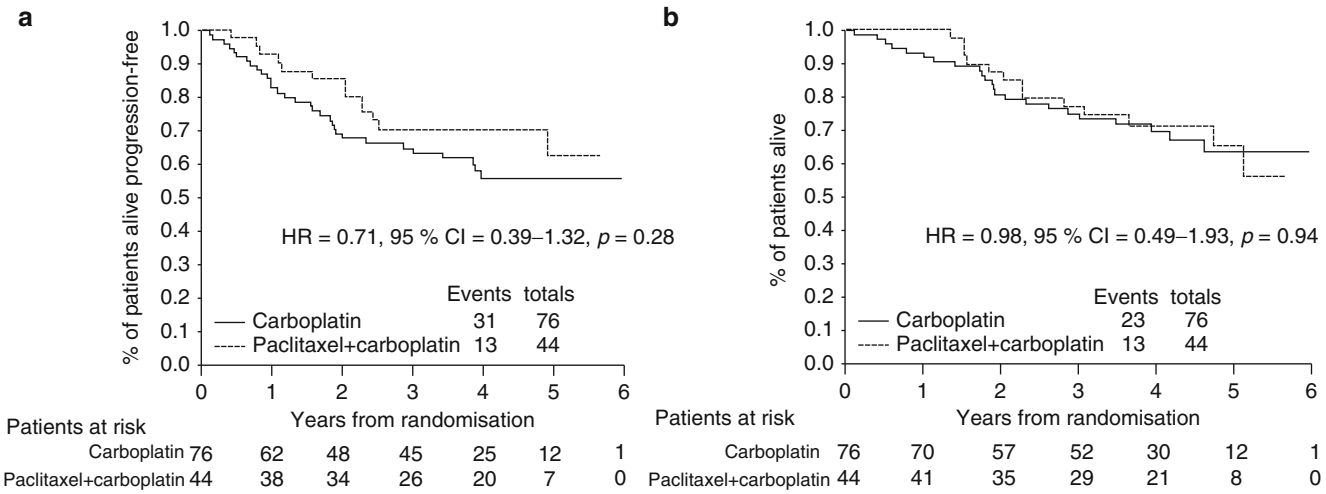

Fig. 1.3 Stage I patients randomized to carboplatin versus paclitaxel + carboplatin in ICON3 trial [73]. (**a**) Recurrence-free survival by treatment arms. (**b**) Overall survival by treatment arms

(Fig. 1.3a). Thirty-six patients have died (13 carboplatin/paclitaxel [30 %], 23 carboplatin [30 %]), and comparison of Kaplan-Meier curves shows no evidence of a difference in OS between the arms (HR = 0.98, 95 % CI = 0.49–1.93, $p = 0.94$) (Fig. 1.3b). The small number of patients leads to wide confidence intervals in the estimates of treatment difference. Some argue that the HR of 0.71 for PFS, despite the wide confidence intervals, supports the use of carboplatin/paclitaxel, whereas others argue that the HR of 0.98 for OS and increased toxicities with doublet therapies supports the use of single-agent carboplatin. In the absence of any prospective comparative randomized trials in this setting, a body of clinicians support the use of less toxic single-agent carboplatin. Further evidence for carboplatin alone comes from a small retrospective study which demonstrated no evidence of a difference in OS between carboplatin and carboplatin/paclitaxel [74]. Two randomized phase III trials have addressed the duration of chemotherapy. GOG 157 randomized 427, surgically staged, stage IA/B, grade 3, stage II, and clear cell women to 3 versus 6 cycles of adjuvant paclitaxel (175 mg/m^2) and carboplatin (AUC 7.5) [75–77]. The primary endpoint was PFS and the median follow-up was 6.8 years. Overall, 71 % of the population had adequate surgical staging and 69 % were stage I. The recurrence risk was 24 % lower in the 6 cycles arm, however, not significantly (HR: 0.76, 95 % CI: 0.51–1.13); similarly, estimated probabilities of recurrence at 5 years and OS were similar between the arms (3 vs. 6 cycles 20 % vs. 25 % and HR 1.02, 95 % CI 0.66–1.57, respectively). Toxicity, as expected, was significantly higher in the longer-duration-treated women. Of interest, in a post hoc analysis of this study by histology, duration of chemotherapy appeared to impact overall survival. When limited to serous histology (23 % of the sample), there was a significant reduction in recurrence with 6 cycles of therapy (HR = 0.33, 95 % CI: 0.14–0.77) in contrast to those with non-serous histology [78]. In the second GOG trial, GOG 175, 571 women with a similar eligibility and staging request were randomized to 3 cycles of paclitaxel and carboplatin or the same regimen with maintenance weekly paclitaxel for 24-week maintenance [79]. The cumulative probability of recurring within 5 years was similar between the arms (23 % observation vs. 20 % maintenance paclitaxel, HR: 0.81, 95 % CI: 0.57–1.15). Similarly, no difference in OS was observed. The maintenance arm was more toxic and led to an approximate 1 % discontinuation per week over the course of therapy. Unfortunately, definitive conclusions cannot be made from GOG 157 due to the ambitious 50 % reduction in recurrence targeted and the relatively small sample size, although due to the limited data in this area this study has impacted on standard practice in North America. Since 3 cycles of therapy appear to be well tolerated and feasible, this may be an appropriate compromise.

Other options for therapy, including adding a third drug (OVAR-9, gemcitabine) or radiation (IP phosphorous-32, whole abdominal radiation), have been investigated in stage I women without demonstrable benefit [80–82].

The issue of additional and maintenance therapy is more controversial and, unfortunately, not completely addressed in the current literature. However, if toxicity precludes additional therapy, the data would support the efficacy of less than 6 cycles. This recommendation is bolstered by the post hoc analysis of the 74 women who recurred after completing therapy in GOG 157 [83]. In this analysis, the median time to recurrence was 21 months. The overall survival after recurrence was only 24 months and was dependent on time to recurrence (10 months for those less than 24 months vs. 35 months for those recurring after 24 months). These data are similar to those with advanced-stage disease and highlight the difficulty of controlling metastatic disease.

Should Intensified Chemotherapy Regimens Including Dose Dense and Intraperitoneal Therapies and Targeted Therapies Be Considered for the Adjuvant Treatment of Early EOC?

Adequately staged and hence true early EOC is associated with higher survival rates compared to more advanced disease. However, even in these early cases, systemic chemotherapy has been shown to improve survival. Thus, it is reasonable to consider whether recent alternatives to standard chemotherapy, such as intraperitoneal (IP) and dose-dense therapy, as well as the impact biological could positively impact outcomes in this cohort of women.

The Case Supporting Alternative (Dose-Dense/IP/Targeted Therapy) Strategies: Evidence

A highly significant improvement of both PFS and OS by merely changing the dose schedule of conventional chemotherapy, without addition of any novel agents, was accomplished by the Japanese GOG group by randomly assigning women with stage II to IV EOC who were randomized to weekly paclitaxel (80 mg/m^2 on day 1, 8, 15) in combination with 3 weekly carboplatin (carboplatin AUC 6 on day 1) [84, 85]. At 6.4 years of median follow-up of 631 eligible women, a highly statistically significant improvement in median PFS in favor of the dose-dense group was achieved compared with to the conventional group (28.1 vs. 17.5 months, [HR] 0.75, 95 % CI, 0.62–0.91; $p=0.0037$). Furthermore OS at 5 years was also higher in the dose-dense group than the conventional group (58.6 % vs. 51.0 %, HR 0.79, 95 % CI: 0.63–0.99, $p=0.0448$) [49, 50]. Even though no stage I women were included, these results could theoretically be extrapolated also to those early EOC women.

Impressive improvements in both PFS and OS have been shown in [86] in 429 women with optimally debulked stage III EOC randomly assigned to intravenous paclitaxel plus cisplatin versus a combination of intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel. The experimental intraperitoneal arm was associated with significantly improved PFS (23.8 vs. 18.3 months, HR=0.80, 95 % CI 0.64–1.00, $p=0.05$) and OS (65.6 vs. 49.7 months, HR=0.75, 95 % CI 0.58–0.97, $p=0.03$) [28] at a median follow-up of 48 months. Remarkably, the OS gain of 15.9 months, at the median, in favor of the intraperitoneal arm was higher than the gain reached when paclitaxel was added to the first-line treatment [75]. Here also, there is a clear hypothesis that the benefit of IP chemotherapy might be projected into earlier stage disease because they are by definition without extra-ovarian disease or, at least, minimal unrecognized extra-ovarian disease. However, the increased toxicity of the schedule should be taken into account and results of confirmatory studies with less toxic schedules awaited.

Biological agents are also attractive in this setting, although the only agent thus far evaluated in early-stage disease has been bevacizumab (ICON7) [14]. However, the hypothesis of the value of maintenance therapy may be linked to small volume/microscopic disease after completing chemotherapy. This has spawned several trials of biological agents in the maintenance setting, such as pazopanib, sorafenib, nintedanib, and erlotinib, as well as several immunotherapy strategies. In ICON7, the addition of bevacizumab to conventional chemotherapy (paclitaxel/carboplatin) resulted in significantly higher PFS and also overall response rates, albeit no improvement of OS. The rate of complete or partial remission was 48 % in the standard-therapy group and 67 % in the bevacizumab group—a highly significant difference of 19 % (95 % CI: 11–28, $p<0.001$) [52]. As opposed to the GOG 218 [87], ICON7 allowed the enrollment of high-risk early-stage disease (9 % of all women). Although a post hoc subgroup analysis was unable to differentiate a benefit in outcome in this cohort, it remains a topic of investigation. The AGO BOOST trial (Ovar 17) is comparing 15- versus 30-month bevacizumab in the maintenance setting, and women with stage IC disease are eligible to participate (NCT01462890).

The Case Against Alternative (Dose-Dense/IP/Targeted Therapy) Strategies: Evidence

While the advances in ovarian cancer adjuvant therapy are impressive, it is tempered by the fact that they rarely included women with early-stage disease and their findings apply in nearly every case to women with advanced measurable residual disease. Since all women with stage I disease are essentially undergoing complete resection (R0), it is a legitimate concern to extrapolate the data to this cohort of women. Even the JGOG dose-dense regimen failed to demonstrate any significant impact on survival in completely resected (R0) cancers [84, 85]. While the ICON7 trial did enroll a small cohort of high-risk stage I women, the benefit of bevacizumab was not evident among this cohort or in those with small volume tumor residuum, but it must be acknowledged that the subgroup was small (capped at 10 % of 1,528 patients). Considering the significantly higher toxicity of bevacizumab, such as hypertension (up to 19 %) and intestinal perforation (3 %), the EMA, which approved this agent in 2012, only licensed its use for stage IIIB and higher. In addition, poor tolerability and high dropout rates prior to completion of therapy in women receiving IP or dose-dense paclitaxel therapy also limit enthusiasm in women with early-stage disease. Furthermore, as stated above, even though in clinical practice both carboplatin and carboplatin/paclitaxel are usually

applied, no clear evidence exists to support the use of combination therapy in stage I disease.

Future Directions: Intensive Dose-Dense/IP/Targeted Therapy

Research efforts try currently to provide answers to a number of important questions relating to treatment duration, the incorporation of new drugs into treatment regimens, and maintenance therapy in advanced disease. The subanalysis of the BOOST (AGO-OVAR 17) trial will enlighten the value of antiangiogenic treatment in stage IC disease. If positive results emerge, then further randomized trials are warranted to prospectively evaluate their role in high-risk early disease.

Future Directions of 1st-Line Chemotherapy in Early EOC

Future clinical trials designed specifically for women with early-stage ovarian cancer are unlikely to be conducted using the current methodology applied to advanced-stage disease due to the small sample size and low risk for recurrence. Patient with high-risk features are increasingly allowed into advanced-stage trials where the strata are evaluated. If development of effective prevention strategies were identified, such as vaccination or novel biological response agents that can reasonably be administered over an extended duration of time, reevaluation would be attractive. However, accurate surgical staging and better interrogation of driving genomic biology will offer new clues into better identifying the risk factors that may help better allocate treatment.

Concluding Comments

- Apparent early-stage epithelial ovarian cancer can present a therapeutic enigma due to a variety of controversial issues including considerations of potential fertility preservation, optimal adjuvant treatment, the value of targeted agents (increasingly utilized in advanced-stage disease), and the appropriate degree of surgical radicality.
- Since most apparent early-stage ovarian cancer patients will have limited disease after formal surgical staging assessment, it is clear that not all patients require surgical castration and, as such, some patients may be amenable to fertility-sparing procedures.
- Equally concerning is under-assessment and under-treatment, which could prove fatal with the development of metastatic recurrence—a clinical scenario that is not easily screened.

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Recurrent Ovarian Cancer: When to Treat and How to Assess

2

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Summary Points

- Role of CA125 in detection of ovarian cancer relapse
- Aims of treatment at different moments of relapse
- Definition of platinum-free interval according to CA125
- Use of CA125 in monitoring patients during maintenance therapy

Introduction

A clinician's goal should be to provide optimal care for ovarian cancer patients in all phases of their disease from prevention to early detection, staging, surgery, chemotherapy, follow-up, and relapse. Over the last several decades, clinical trial results have led to an evolution in the management of ovarian cancer [1]. The majority of women who present with advanced ovarian cancer will complete standard cytoreductive surgery and chemotherapy and enter a phase of follow-up and ultimately relapse. Fortunately, there are many therapeutic options available once a woman has relapsed including secondary cytoreductive surgery and at least seven active chemotherapeutic or biological agents. Despite the available therapies, long-term survival is currently rare once a patient has relapsed. Nonetheless, treatments in the recurrence setting have been shown to improve both progression-free (PFS) and overall survival (OS) [2, 3]. Different approaches to following patients and diagnosing relapse (Table 2.1) can make a significant difference as to when the relapse is diagnosed and how patients are managed. This chapter explores these different approaches and their implications.

Aims of First Line of Treatment

There is increasing evidence that patients with no macroscopic cancer remaining after either initial or interval cytoreductive surgery are those most likely to be long-term disease-free survivors [6]. Since the majority of women present with advanced-stage disease, only a minority of patients with ovarian cancer can be cured. A 5-year relative survival is approximately 20–30 % for stage III and 5–10 % for stage IV disease [7]. The aim of screening programs and educating doctors to diagnose ovarian cancer early is to increase the fraction of patients diagnosed with stage I disease, where long-term disease-free survival is expected in over 80 %.

For first-line treatment, the aim is curative and clinical trials have established paclitaxel plus carboplatin as the primary intravenous treatment strategy for epithelial ovarian cancer [1]. A study by the Gynecologic Oncology Group (GOG) demonstrated a survival benefit of cisplatin and paclitaxel in comparison to cisplatin and cyclophosphamide [8]. This was followed by GOG 158, which demonstrated that

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Table 2.1 Comparison of timing and assessment of follow-up according to NCCN [4] and ESMO [5] clinical guidelines

	Frequency	Time after diagnosis	History and physical exam	CA125	Imaging	Self-reported symptoms
NCCN	Every 2–4 months	0–2 years	Yes	*NCCN*: every visit if initially elevated discuss pros and cons of monitoring with CA125	CT. If signs of progression according to clinic and CA125	*NCCN*: educated in symptoms
ESMO	Every 3 months	0–2 years				
NCCN	Every 3–6 months	3–5 years			*NCCN* PET. If clinically indicated (lower level of evidence than CT)	
ESMO	Every 4 months	third year		*ESMO*: adequate toll Offer women informed choices	*ESMO* PET. If potential candidate for surgery superior to CT scans in detecting more sites of disease	*ESMO*: not specified
NCCN	Every year	Until progression				
ESMO	Every 6 months	4–5 years or until progression				

CT computer tomography, *PET* positron emission tomography

carboplatin plus paclitaxel is at least as effective as cisplatin plus paclitaxel, but with less toxicity [9]. However, the ICON3 trial demonstrated that single agent is as effective as carboplatin plus paclitaxel with regard to both OS and PFS but has a more favorable toxicity profile. While the international standard for first-line therapy is carboplatin and paclitaxel, some physicians believe that single-agent carboplatin is a reasonable option as first-line chemotherapy, particularly in patients with marginal performance status [10].

Additional agents such as topotecan, gemcitabine, and pegylated liposomal doxorubicin, which have been evaluated either as a part of triple-drug therapy or in sequential doublets, failed to demonstrate superiority over carboplatin plus paclitaxel [11]. In a recent randomized phase III trial, a dose-dense regimen of weekly paclitaxel in combination with carboplatin every 3 weeks showed a statistically significant improvement in progression-free survival (PFS) (28.0 vs. 17.2 months) and overall survival (OS) at 3 years (72.1 vs. 65.1 %; HR = 0.75, CI 0.57–0.98) compared to standard 3-weekly dosing of both agents [12]. However, confirmatory studies are awaited, since 13 other randomized dose-intensity studies in first-line therapy did not report such a large difference in PFS and OS [13].

Recently, the addition of bevacizumab has been shown to increase PFS by 2–4 months when added to first- or second-line chemotherapy and continued as maintenance treatment in randomized phase III trials. In a subgroup of stage III suboptimally debulked and stage IV patients, it has been shown to improve survival by 8 months [14–16]. It seems sensible to consider prioritizing first-line bevacizumab for patients who are at high risk of having a short PFS as the bevacizumab might delay symptoms and these "platinum-resistant" patients are unlikely to have an opportunity to receive bevacizumab as part of second-line treatment [16].

Aims of Relapse Treatment

Once ovarian cancer relapses after first-line chemotherapy, only a small fraction of patients survive more than 5 years. The aim of treatment in recurrent ovarian cancer is to prolong PFS and OS and/or to eliminate or reduce symptoms and maintain or improve quality of life [3, 17]. The longer the interval between treatments, the more likely the disease is to respond to retreatment with the same drugs [18]. Decision making is based primarily on whether patients are categorized as having "platinum-sensitive" or "platinum-resistant" disease [19]. The combination of platinum plus paclitaxel has shown significant improvements in PFS and OS vs. single-agent platinum [20], while the combination of pegylated liposomal doxorubicin plus carboplatin was shown to be non-inferior to carboplatin plus paclitaxel. Median PFS was 11.3 vs. 9.4 months, respectively, with a hazard ratio of 0.56 (95 % CI 0.48–0.65) for a therapy-free interval >12 months vs. 6–12 months [21].

Currently, there are at least seven conventional agents that can be used sequentially to treat recurrent ovarian cancer. A significant minority of patients respond to multiple agents, including the repeated administration of platinum-based chemotherapy. Patients with a deficiency of homologous DNA repair from germ line mutations or other somatic lesions ("BRCAness") may enjoy better survival [22] related to better response to therapy for recurrent disease [23]. Few studies have analyzed the efficacy of third-line chemotherapy. In one retrospective study, up to 50 % of relapsed ovarian cancer patients were treated with third-line chemotherapy with 40 % response rates and a median overall survival of 10.4 months [24]. Another retrospective study reported low efficacy of chemotherapy with successive lines of treatment in "platinum-resistant" disease, leading the authors to suggest that chemotherapy should be discontinued if patients' disease progressed on two consecutive lines of cyto-

Table 2.2 Factors that may contribute to doctor–patient disparity [26] in understanding of prognosis

Physician factor	Patient factor
Reluctance to disclose prognosis	Ambiguous attitude to knowing prognosis
Low confidence in ability to prognosticate accurately	Denial
Low confidence in ability to discuss prognosis	Distress
Insufficient time	Preferring to entrust details to experts
Fear of destroying hope	Fear of causing offense by questioning
Fear of provoking emotional distress	Fear of wasting the physician's time
Fear of being blamed	Fear of losing hope
Fear of confronting own emotions	Cultural expectations
Fear of confronting death	Difficulty understanding terminology or certain information formats
Feelings of inadequacy	
Burnout and compassion fatigue	
Cultural expectations	
Overestimation of patient understanding	

toxic treatment. This study identified several factors associated with worse outcome at the time of platinum-resistant diagnosis including poor performance status, presence of stage IV disease, elevated CA125, and platinum-refractory disease [25].

Should Patients Be Told About the Different Aims of First-Line Treatment and Treatment for Relapse, and if Yes, When During Their Patient Journey Should They Be Told?

It is standard practice that when patients start first-line therapy, they are told about the aims and likely outcome with associated side effects. One should explain to the patient that we are currently able to cure most women with early-stage ovarian cancer, and even a minority of those who present with advanced disease. There is a far greater difference between doctors as to what patients are told about the aims of follow-up and the likely outcome of treatment for relapse (Table 2.2). The Society of Gynecologic Oncologists issued a statement advising that patients and their physicians "actively discuss the pros and cons of CA125 monitoring and the implications for subsequent treatment and quality of life".

There are differences in opinion as to whether we have adequate data to confirm or refute that close follow-up benefits women with ovarian cancer. Dr. Bast describes in this chapter what he considers are methodological limitations in trial design, which make it difficult to conclude whether optimal monitoring with CA125 and optimal current therapy would impact on survival. In this setting, whether or not to monitor with CA125 should be discussed with each patient. Following worldwide presentation and discussion of the MRC OVO5/EORTC 55955 CA125 follow-up trial [27], it is the opinion of Dr. Rustin that those who argue most passionately in favor of routine testing are those who are least likely to inform patients at completion of first-line therapy that therapy for relapse is rarely curative. Dr. Bast agrees that a full discussion with each patient regarding whether or not to monitor with CA125 is essential, but is unaware of data to support Dr. Rustin's assertion regarding physician behavior.

Table 2.3 Obstacles to achieve patient-centered cancer treatment planning [29]

Family related	Patient related	Physician related
Family dynamics	Lack of assertiveness	Lack of time to explain complex information
	Health literacy	Lack of tools to facilitate treatment planning
	Health numeracy	Insensitivity to patients' needs informational cultural emotional
	Emotional state	
	Concurrent illness	

Should Information About CA125 Be Disclosed at the End of the First-Line Treatment?

A good time to start discussion about the options in management after completion of the chemotherapy is when women are evaluated to receive their last one or two courses of first-line chemotherapy. It is difficult to discuss follow-up procedures with a patient (Table 2.3) unless they are told what the aims of follow-up are. If they expect cure from relapse therapy, they will obviously want intense surveillance as part of follow-up. Some patients will not want additional aggressive therapy and may wish to avoid the anxiety associated with monitoring using CA125. Other patients will want to be monitored to allow time to plan their lives and to utilize multiple conventional and novel therapies should disease recur.

Patients, on the average, live longer from first relapse to death than from diagnosis to first relapse, so at this point it is

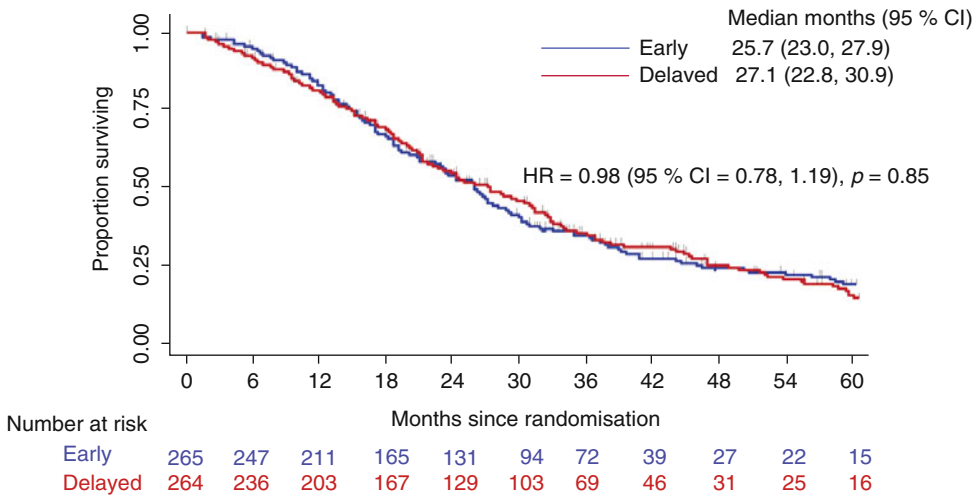

Fig. 2.1 Kaplan–Meier plot for overall survival in the OV05/55955 trial. Median survival from randomization was 25.7 months (95 % CI 0–27.9) for patients on early treatment and 27.1 months (95 % CI 22.8–30.9) for those on delayed treatment [28] (Reprinted courtesy of Elsevier)

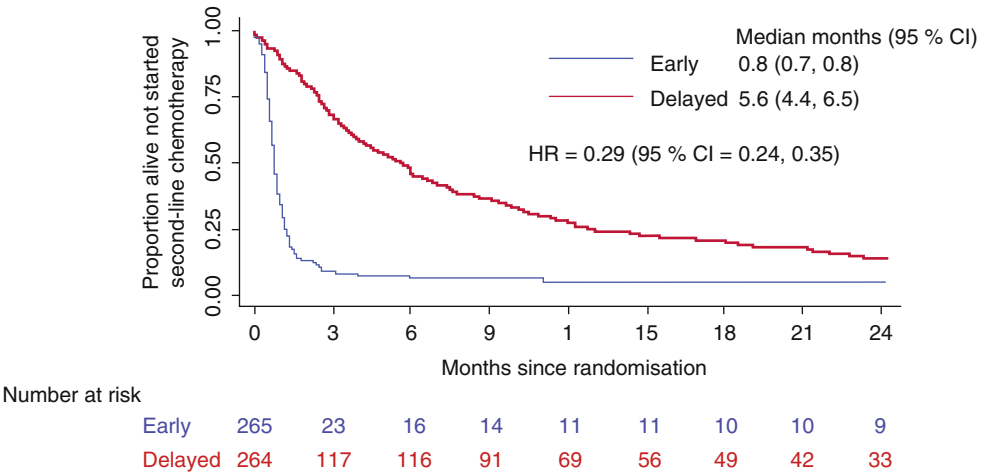

Fig. 2.2 Kaplan–Meier plot for second-line chemotherapy in the OV05/55955 trial. In those patients treated upon a rising CA125, treatment was started a median of 4.8 months earlier [28] (Reprinted courtesy of Elsevier)

important to inform ovarian cancer patients that while many women die within a year of symptomatic relapse, others can live several years even after their cancer has come back due to improvements in treatment of relapsed disease.

Does Earlier Detection of Recurrence Matter?

No

Ovarian cancer is one of the few cancers where rising levels of a circulating tumor marker can lead to diagnosis of relapse months and sometimes years before signs or symptoms of relapse develop [29]. Until recently, a woman with a rising level of CA125, who remains well without symptoms or signs of recurrent disease, has presented a major management dilemma. In some cases retreatment was made on the basis of CA125 alone as it was thought that early treatment would lead to an improvement in outcome. In other cases, decisions were based more on clinical symptoms or radiological changes [3].

Data from the few randomized studies that have investigated timing of therapy in cancers other than ovarian [30–34] provide conflicting data about the benefit of early treatment for patients presenting with metastatic disease, and no randomized trials have adequately addressed timing of treatment for recurrent cancer [35, 36].

The uncertainty about the appropriate timing of reintroducing chemotherapy prompted a trial conducted by the MRC and EORTC, OV05/55955, which compared retreatment based on a doubling of CA125 above the upper limit of normal with treatment determined by conventional clinical assessment [27].

In this randomized controlled trial, 1,442 women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA125 concentration were registered, of whom 529 were randomly assigned to treatment groups (265 early treatment upon CA125 rise, 264 delayed treatment upon clinical or symptomatic relapse) when CA125 concentrations exceeded twice the upper limit of normal.

There was no evidence of a difference in OS between early and delayed treatment (HR 0.98, 95 % CI 0.80–1.20), (p=0.85 median survival from randomization was 25.7 months (95 % CI 0–27.9) for patients on early treatment and 27.1 months (22.8–30.9) for those on delayed treatment (Fig. 2.1)). In those treated upon a rising CA125, treatment was started a median of 4.8 months earlier (Fig. 2.2). The results of this trial provide

Table 2.4 Definitions and time from biochemical progression to clinical progression [28, 38, 40–43]

	Range	Published	Author	Year	Number of patients	Biochemical definition	Detection before clinical relapse (months)
First relapse	Normal	Gynecol Oncol	Wilder	2003	11	3 consecutive elevations	14 (4–24)
		JCO	Santillian	2005	39	Elevation 10 U/ml or 100 % compared to nadir	No data
Second relapse	Doubling	Ann Oncol	Rustin	1996	255	Doubling upper limit of normal	2
		Ann Oncol	van der Burg	1990	49	Elevated CA125 level	4.5
		JCO	Rustin	2006	254	CA125 GCIG criteria	1.8
		Lancet	Rustin	2010	529	Doubling upper limit of normal	4.8
		Lancet	Rustin	2010	464	Doubling upper limit of normal	4.6

no evidence that early initiation of chemotherapy because of a rising CA125 concentration improves survival.

It has been shown that if a rise of CA125 within the normal range is also used to define progression, the lead time between CA125 rise and progression is longer than the 4.8 months found in the OVO5/55959 trial [37]. If there had been a hint of improved survival in the early arm of that trial, it could be postulated that if diagnosis of relapse could be made earlier, then survival would be even longer. However as there was absolutely no hint of improved survival in the early arm of OVO5/55959 trial, using more sensitive CA125 definitions for relapse is very unlikely to prolong survival, but will lead to patients spending more of their remaining life aware that their cancer has relapsed.

This trial also showed that a deterioration in quality of life scores was seen sooner in the early group than in the delayed group, and there was evidence of significant disadvantages for role, emotional, social, and fatigue subscales in the early group. The OVO5/55955 trial almost certainly underestimated the deterioration in quality of life due to the earlier introduction of chemotherapy as the quality of life forms used asked about quality of life during the previous week. As most patients received 3-weekly chemotherapy and the forms were completed just prior to the next course, the worse side effects of the chemotherapy are by then likely abated.

In summary, there is no evidence that earlier treatment of recurrent ovarian cancer is beneficial.

Yes

The value of early detection of recurrence depends upon the effectiveness of therapy. Traditionally, close follow-up after primary therapy has been based on the assumption that detecting small volumes of recurrent disease will improve subsequent management. In the case of cancers at different sites where metastases can be excised or are exquisitely sensitive to chemotherapy such as colorectal cancer and gestational trophoblastic disease, close surveillance can provide a second chance to achieve long-term survival.

In the case of ovarian cancer, treatment of recurrent disease with a combination of drugs can prolong PFS and OS with a small fraction of patients surviving >5 years. Recurrent disease can also be treated with secondary cytoreductive surgery if it is still small in volume at the time of detection. In a recent retrospective case-control study involving 121 patients with a complete response following primary therapy, the overall survival post-recurrence diagnosed by surveillance testing (82 %) vs. symptoms (18 %) was significantly prolonged for asymptomatic patients (71.9 vs. 50.7 months; $p=0.004$) [38]. Although no difference in the percentage of patients undergoing secondary cytoreductive surgery was observed between the two groups, optimal residual disease was higher in the asymptomatic recurrence group (90 vs. 57 %; $p=0.053$).

Only the MRC OV05/EORTC 55955 trial has addressed prospectively whether early detection of recurrent disease improves overall survival or quality of life [27]. Rustin and colleagues deserve high praise for undertaking an ambitious clinical trial with the goal of testing whether earlier detection of recurrence actually impacts on outcome. Their large randomized trial found no survival advantage to treating 4.8 months prior to clinically obvious symptomatic recurrence. A rising CA125 proved to be a reliable biomarker for detecting recurrence in the majority of women, but relapse therapy was equally effective palliation whether given early or late. Unfortunately, the trial took 9 years to complete. Over nearly a decade, methods for monitoring CA125 improved and the standard of care for treatment of recurrent disease had changed [27]. In addition, the two study arms may not have been balanced for cytoreductive surgery, one of the most important prognostic variables, or for persistent disease following chemotherapy, as consistent CT imaging was not performed prior to study entry.

Criteria for using CA125 to detect recurrence have changed over the years. In the MRC OV05/EORTC 55955 trial, Rustin et al. had defined relapse as doubling outside the normal limit for CA125 based on earlier studies listed in Table 2.4. Using this standard, recurrence can be detected in approximately 70 % of patients with a lead time of 3–4.8 months. Over the last decade, new studies have shown that persistently rising CA125 within the normal range has up to 94 % specificity for detecting recurrence with a mean lead time of 6 months and a range of 2.8–17 months (Table 2.4). Algorithms have been developed to screen for primary ovarian cancer, and early-stage, small-volume

disease has been detected within the normal range. Such algorithms have not yet been applied to detecting disease recurrence, but are likely to extend lead time by additional months.

Of greater concern, as described in detail below, is that treatment on MRC OV05/EORTC 55955 was at the discretion of the participating physician. Consequently only 25 % of patients received an optimal combination of a taxane in addition to a platinum compound within 1 month of discovering a rise in CA125. Suboptimal therapy given earlier is still suboptimal and unlikely to impact on survival.

Should Patients Be Monitored with CA125 Measurements After Completing First-Line Treatment?

Yes

Rising CA125 can detect recurrent disease several months prior to symptomatic relapse with substantial specificity. As a biomarker to detect recurrence of ovarian cancer, CA125 values can rise outside the normal range 3–4.8 months before symptomatic recurrence in approximately 70 % of patients. Over the last decade, studies have shown that rising CA125 within the normal range has up to 94 % specificity for detecting recurrence with a mean lead time of 6 months and a range of 2.8–17 months (Table 2.4). Crawford and Peace [43] analyzed the time to biochemical progression in 79 patients who reached values of CA125 <30 U/ml following chemotherapy. The median time to biochemical progression was 81 months in the patients with CA125 nadir ≤10 U/ml, 6 months in those with nadir of 11–20 U/ml, and 3 months in those with nadir of 21–30 U/ml ($p<0.001$), and the corresponding median overall survival was 98, 18, and 18 months ($p<0.001$). Recent studies suggest that groups of patients with different risks of relapse can be readily identified following first-line therapy. Since patients with ovarian cancer often have the same schedule for follow-up independent of their stage, follow-up might be personalized according to CA125 nadir, an approach suggested some years ago to avoid the then commonly performed second-look surgery [44]. Factors that could be considered include the initial stage, degree of cytoreduction, and the CA125 nadir following treatment. Patients with early-stage disease, optimal cytoreduction, and a low CA125 nadir might be followed at longer intervals.

No

The ESMO guidelines suggest history and physical examination including pelvic examination every 3 months for 2 years, every 4 months during the third year, and every 6 months during years 4 and 5 or until progression is documented [5]. They conclude by stating that there is no benefit from early detection of relapse by routine CA125 measurement and that it is important to offer women informed choices in follow-up and keep in mind that a potentially resectable occult macroscopic recurrence can be signalled by a CA125 rise.

Patients need to be told about the MRC OV05/EORTC 55955 trial [27] to help them choose their preferred follow-up option. They need to be told that CA125 monitoring does not confer a survival advantage and that even if they opt to have regular CA125 monitoring, they are aware that a rising level, though signifying they have relapsing disease, does not necessarily mean they require immediate chemotherapy.

An alternative recommendation is not to have routine CA125 measurements performed, provided they are well and have no symptoms to suggest relapse. Patients can be given an information sheet detailing what symptoms they should look out for that should prompt an early appointment and how to access the oncology team rapidly to have their CA125 level measured.

Patients should be given the choice of having regular CA125 measurements, which they might want for a variety of reasons that include having more control over their lives, more warning of when they might need more therapy, reassurance, or because their physician recommends it.

Should the Timing of Treatment of Relapse Differ Between First and Later Relapses?

No

For this discussion we are assuming that the correct decision for first relapse is to delay therapy until symptoms. There appear no good reasons to doubt this conclusion. Although slightly more patients in the delayed arm of MRC OV05/EORTC 55955 received taxanes on relapse, the numbers are too few to have dramatically improved survival in the delayed arm, and there was no difference between those treated before or after the results of ICON4 became available. If earlier therapy of first relapse cannot prolong survival, it is inconceivable that early treatment of second or later relapse could improve survival. Interestingly women assigned to early second-line treatment needed third-line treatment for clinical progression on average 4.6 months (95 % CI 4.2–5.8) earlier than those assigned to delayed second-line treatment (Fig. 2.3), thus not benefiting from earlier treatment. One big difference between patients on follow-up after first-line or relapse therapy is that many of those after first line live in hope of having been cured, while all patients who have relapsed once should be aware that they will relapse again. Therefore some patients who were happy not to have CA125 measurements during initial follow-up want them following relapse so that they can time their next line of chemotherapy to fit in with their plans.

Yes

Perhaps the greatest limitation of the MRC OV05/EORTC 55955 study was that treatment of recurrent disease was not defined by the protocol. Whether to treat, when to treat, and which drugs to prescribe were all at the discretion of the individual participating physicians. Some 66 % of patients did not receive paclitaxel chemotherapy, despite the fact that ICON4 had shown superior progression-free ($p=0.0004$) overall

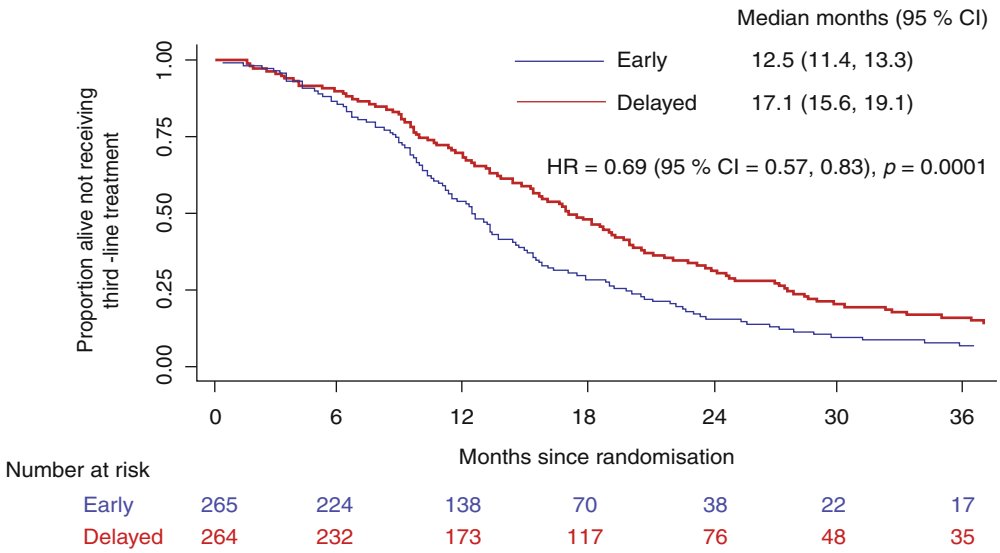

Fig. 2.3 Kaplan–Meier plot for third-line chemotherapy in the OV05/55955 trial. Women assigned to early second-line treatment needed third-line treatment for clinical progression on average 4.6 months (95 % CI 4.2–5.8) earlier than those assigned to delayed second-line treatment [28] (Reprinted courtesy of Elsevier)

(p=0.02) survival with a combination of carboplatin and paclitaxel when compared to carboplatin alone in the same, largely United Kingdom, patient population in the 1990s. Moreover, 23 % of patients were started after a delay of more than 1 month or were never treated. Given only 4.8 months of lead time, delays of more than a month are likely to minimize any benefit of "early" treatment. Consequently, only 25 % of participants were treated promptly with therapy that would prolong survival. In addition, only 7 % of patients underwent secondary surgical cytoreduction. As described below, this procedure has been associated with improved survival in many, albeit retrospective, studies, and secondary cytoreduction is most feasible with small volumes of disease. Consequently, most patients in this trial did not receive optimal state-of-the-art treatment by current standards. It should not be surprising that somewhat earlier administration of inadequate therapy did not improve survival.

Whether or not there is a survival advantage with earlier treatment for the average patient, earlier detection of recurrence does permit time to be treated with the many conventional agents known to have activity as well as with novel targeted agents. Further, a decision to forgo monitoring based on currently available therapy for recurrent disease assumes that there will be no advance in therapy over the next several years.

Once disease recurs, the international standard of practice is to monitor response or lack of response with CA125 and imaging in order to detect progression and spare patients the unnecessary toxicity of ineffective treatment,

Does Secondary Cytoreductive Surgery Benefit a Subset of Patients with Recurrent Disease?

Yes

A meta-analysis of 2,019 patients [45] found the only variable related to survival was the fraction of patients undergoing complete secondary cytoreductive surgery. The smaller the tumor burden, the greater the number of potential candidates for resection [46]. Several retrospective studies have tried to identify the best candidates for secondary cytoreduction. Chi et al. [47] identified disease-free interval (DFI), number of disease sites, and less than 0.5 cm of residual disease as prognostic factors for overall survival consistent with the data published by Salani et al. [48]. This group described in this multivariate analysis DFI over 18 months, 1–2 sites of disease, and no macroscopic residual disease as positive prognostic factors. The AGO group in the DESKTOP study [17, 49] identified and validated good performance status, no residual disease after surgery for primary treatment, and ascites <500 ml in preoperative diagnostics as predictors of complete resection, achieving 79 % of complete cytoreduction if they fulfilled the three criteria. Other factors identified include low or normal CA125 levels [50] and lack of symptoms [38].

Fleming et al. [51] have recently reported 74 patients who underwent secondary cytoreductive surgery that was optimal (<0.5 cm) in 41 and suboptimal in 33. Optimal cytoreduction was associated with longer disease-free survival (19 vs. 12 months) and longer overall survival (47 vs. 23 months, p<0.0001). Patients who attained optimal secondary cytoreduction went to surgery sooner after a rise in CA125 twofold from nadir (5.3 vs. 16.4 weeks). Each week delay after the first CA125 elevation correlated with a 3 % increased chance of suboptimal surgery.

No

The role of surgery in the relapsed setting remains controversial. There are no randomized data demonstrating a survival advantage from undergoing secondary cytoreductive surgery in the relapse setting. A number of retrospective studies have reported good PFS in patients who have undergone optimal secondary debulking to no macroscopic residual disease. As highlighted by Bast and colleagues above, Chi et al. reported from the Memorial Sloan–Kettering Center that

median survival in patients undergoing secondary surgery achieving ≤0.5 cm residual disease was 56 vs. 27 months in those who had residual disease ≥0.5 cm ($p<0.01$) [47]. Fleming and colleagues reported a longer OS in a retrospective analysis at their institution following optimal vs. suboptimal secondary cytoreductive surgery [51]. The optimal group had surgery an average of 5.3 weeks after their rising CA125 was noted compared to 16.4 weeks in the suboptimal group. One wonders why the group who had suboptimal debulking had to wait so much longer to undergo surgery compared with the optimally debulked group (5.3 weeks). Could it be that the group with a longer delay did not have obvious operable disease on initial scanning at the time their CA125 rose, and in fact had more widespread but less visible disease? Interestingly, a small Japanese study recently showed that earlier surgery prompted by rising CA125 levels had a worse survival than those who underwent secondary surgery based on symptoms and routine clinical examination and imaging [52].

DESKTOP 3 (NCT01166737) and GOG213 (NCT00565851) are current randomized trials investigating the role of further surgery in the relapsed setting. While we wait for these trials, it is possible to select a large group of patients who would not benefit from secondary surgery and who therefore could not benefit from regular CA125 measurements. DESKTOP 1 and 2 inform us that patients with suboptimal primary cytoreductive surgery, ascites, and an ECOG performance status of ≥1 rarely achieve optimal secondary surgery [17, 53]. Most gynecologic oncologists would not recommend further surgery for patients with a relapse-free interval of under 6 months and many if less than12 months because these tumors are likely to relapse quickly again. Advocating routine CA125 surveillance to detect surgically resectable disease cannot be justified for most patients, but a case could be made for performing CA125 measurements and CT scanning in a select group of patients who remain symptom free at least a year after optimal surgery and first-line chemotherapy.

Should Patients Be Monitored Only by Symptoms After Completing Later Lines of Treatment?

Yes

It has already been discussed that earlier treatment of later lines of treatment is unlikely to prolong survival. Patients should be given the same options as they were offered after first-line therapy. A big difference in following patients who have already relapsed is these patients should be aware that they are bound to relapse again. This might prompt some to want an advance warning from a rising CA125, of the need for more therapy. Others might prefer to enjoy life while they are symptomatic without being worried by the knowledge of a rising CA125 level.

No

It is important to monitor both symptoms and CA125. On average, women with ovarian cancer only survive 12–18 months following symptomatic relapse [54]. A small fraction survives greater than 5 years after responding to multiple drugs individually and in combination. Currently there are seven active drugs that are generally given sequentially, requiring 2–3 months to evaluate the response to each. Waiting for symptomatic recurrence will limit the number of agents that can be given and the chance for longer survival. In relapsed ovarian cancer, improved performance status is regarded as a prognostic factor of response to chemotherapy [25] and to surgery [46]. If only symptomatic patients were treated, outcomes with optimal conventional chemotherapy are likely to be compromised.

The MRC OV05/EORTC 55955 trial underlines the urgent need for more effective therapy [54]. At present there are >400 new agents being developed to treat cancer. Combinations will almost certainly be required. In the United States less than 4 % of patients enter trials and only half of ovarian cancer patients may have readily measurable disease. Waiting for symptomatic recurrence is likely to further reduce the number of women willing and capable of participating in clinical trials, further slowing progress.

Should Monitoring Differ Between Patients on Clinical Trials and Those Not on Clinical Trials and How Does the Monitoring Influence Clinical Trials?

Methods and intervals for follow-up must be defined and prespecified in every clinical trial protocol. If accurate measurement of time to progression is required, then monitoring is likely to include CT or MRI scans using RECIST 1.1, CA125 by the CCIG criteria, or newer techniques such as PET imaging. Sensitivity reported for imaging techniques in ovarian cancer range from 40 to 93 % [55]. Computerized tomography (CT) is reproducible, widely available and well understood, and belongs to initial work-up of ovarian cancer staging in guidelines [56]. Nevertheless correlation between CT and surgical findings after optimal cytoreduction is only 57 % although this discordance was not an independent prognostic factor for overall survival [57]. There are emerging data that PET/CT may help in the assessment of patients with elevated CA125 but negative imaging findings. PET/CT is useful in assessing persisting ovarian cancer and serves as a complementary imaging technique when CT or MRI findings are inconclusive or negative [58].

In most ovarian cancer trials, routine CA125 measurements are a mandatory part of the follow-up protocol. To reduce anxiety generated by waiting for and then being told their CA125 result, patients could elect not to be told the results of their CA125 measurements if they remain asymptomatic. While patient and physician attitudes can certainly

differ between countries, in the United States, most patients would want to know the results of all their tests including CA125 and have a right to access to these data. Studies have indicated that patient education can significantly reduce anxiety regarding biomarker results.

If patients are not in clinical trials, the strongest argument for routine scans relates to finding patients suitable for secondary cytoreductive surgery, as discussed above. Many of the arguments posed above for use of CA125 in detecting recurrence could apply to scans as well, but given the expense, inconvenience, and radiation exposure, scans could be prompted by rising CA125 in those patients who choose to be monitored. At present, there is no consensus regarding the use and frequency of scans for follow-up.

The Problem of Defining Platinum Resistance with CA125

The Gynecologic Cancer Inter Group (GCIG) definition is commonly used to define relapse according to CA125, based on a confirmed doubling from upper limit of normal, or baseline if higher [59]. Regular CA125 measurements lead to an earlier diagnosis of relapse, which will result in a shorter PFS. It is essential in randomized trials that a similar frequency of measurements is performed in both arms. The greatest problem arises in defining "platinum resistance." Patients who have routine CA125 measurements will be diagnosed as relapsing weeks to months earlier than if they waited for symptoms or even had routine scans. Thus a patient who had a CA125-defined relapse at 4 months and was considered "platinum resistant" might not relapse with measurable disease until beyond 6 months and then would be defined as "platinum sensitive." It is therefore essential to record how relapse is defined and many protocols now exclude patients as being "platinum resistant" purely because of CA125 measurements. However despite the method of relapse detection being recorded, results of treatment of patients with "platinum-resistant" tumors can be biased. Centers that recommend routine CA125 measurements are likely to enter better prognosis patients into "platinum-resistant" clinical trials than centers that diagnose relapse only after symptoms develop.

Should Maintenance Treatment Affect Monitoring?

An increasing number of patients are likely to receive maintenance therapy with antiangiogenic agents such as bevacizumab following the positive results of GOG218, ICON7, and OCEANS trial [14, 15, 60]. These patients are likely to receive maintenance therapy either for a defined period or until progression. The implications of performing routine CA125 measurements or scans need to be appreciated. In an individual patient it is unclear whether rising CA125 levels indicate failure of the therapy, as the level could be rising much slower than if they were not on that therapy. Patients could be prematurely taken off treatment as a result of a rising CA125 when they may still be deriving clinical benefit. On the other hand, measuring and noting a rising CA125 can indicate disease progression and signal discontinuation of maintenance treatment if recurrence is confirmed by imaging, minimizing side effects, and the cost of the drugs.

Conclusions

Treatment decisions, staging work-up, as well as follow-up should be informed by the results of controlled clinical trials that measure hard outcomes and quality of life. We must also consider likely advances in the future, respect our patient's right to know their disease status, and provide as many options as possible for them to participate in the management of their illness.

The benefit of surgically treating small-volume, recurrent disease remains to be established prospectively, although retrospective studies suggest that it benefits a subset of patients. The results of GOG213 and DESKTOP III are eagerly awaited but will not be available for years. As targeted therapy continues to develop, the addition of novel drugs in combination with cytotoxic chemotherapy or as single agents could provide more effective palliation and improve overall survival. Rustin and colleagues have argued that unless earlier treatment in the relapsed setting can show an overall survival benefit, routine CA125 monitoring is not necessary and may lead to earlier and more lines of treatment, impacting negatively on quality of life in this palliative setting. Bast and colleagues, on the other hand, assert that monitoring with CA125 will detect disease at least 4.8 months earlier than symptomatic recurrence. Using a rise in CA125 levels within the normal range, patients could lead to the start of conventional or experimental therapy several more months earlier.

Whether to monitor CA125 is, however, a decision that must be individualized with appropriate and realistic counselling. Patients need the facts with both sides of various arguments put forward. From here the patient and oncologist can have a platform on which to base future consultations and treatment directions.

Concluding Comments

- Role of secondary cytoreduction is yet to be established prospectively and the role of CA125 in patient selection.
- CA125 modifications over time even within normal range might help detect relapses even earlier than by conventional GCIG criteria.

- As ovarian cancer heterogeneity at a pathologic and molecular level is established, a combination of biomarkers according to the tumor subtype at the moment of diagnosis might prove useful.
- Both CA125 and imaging must be used in deciding whether to stop maintenance therapy following first-line treatment.
- If therapy is developed for recurrent disease that is shown to improve survival, monitoring patients in remission with biomarkers and scans will become more important.

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New Views of Ovarian Carcinoma Types: How Will This Change Practice?

3

Martin Köbel, Robert J. Kurman, and Jeffrey D. Seidman

Summary Points

- Recent knowledge gain of the molecular underpinning of ovarian carcinomas has dramatically changed our understanding of this disease with respect to precursor lesions and subclassification.
- Refined criteria have enabled a more reproducible histological typing by morphology alone.
- Several biomarkers have been proven to be of value to enhance the reproducibility of typing.

Introduction

It has recently become clear that heterogeneity of ovarian carcinomas is not only a matter of extent, i.e., localized or advanced disease but that ovarian carcinoma actually comprises a group of biologically distinct diseases. The heterogeneity between individual tumors can be seen in almost any aspect, e.g., with respect to precursor lesions, molecular alterations, morphology, and clinical behavior [1]. An important question now is: what is the best way to subclassify ovarian carcinomas? The first split in a hierarchical biological classification system could be based on either the cell of origin or oncogenic alterations.

The identification of key molecular drivers such as BRCA1/2 has enabled researchers to identify the precursor for the most common type of ovarian carcinoma, high-grade serous carcinoma, which now appears likely to derive from the distal fallopian tube (fimbriae) and not from the ovarian surface epithelium as previously expected [2–5]. Further evidence suggests that endometrioid and clear cell carcinomas arise from endometriosis [6, 7], and even low-grade serous and mucinous carcinomas may not originate from the ovarian surface epithelium [8, 9]. Molecular studies have revealed that *TP53* mutations are ubiquitous in high-grade serous carcinomas but absent in low-grade serous carcinomas [10, 11]. *ARID1A* mutations are confined to endometrioid and clear cell carcinomas [6, 7]. Hence, different cells of origin show different susceptibilities to certain oncogenic alterations. However, these oncogenic alterations are not entirely specific for a given type. Carcinomas arising from fallopian tube-type epithelium can develop along diverse pathways to high-grade serous or low-grade serous carcinomas [9]. Other molecular alterations can span across different cell types such as *KRAS* mutations that occur in mucinous and low-grade serous carcinomas [12, 13]. Nevertheless, these studies favor a model in which the cell of origin determines oncogenic alterations, which coalesce in a certain phenotype: the histological type. Histological types of ovarian carcinomas are different diseases if epidemiological factors, cell of origin, molecular alterations, biomarker expression, clinical behavior, and morphology are considered. Table 3.1 gives an overview of selected characteristics of the five major histological types: high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous carcinomas.

The parsing of ovarian cancers by histological type is one of two complementary viewpoints of the pathogenesis and biology of ovarian carcinomas. A recent proposal separates ovarian carcinomas into type I and type II pathogenetic categories [9, 14]. Type I tumors grow slowly and have an indolent

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Table 3.1 The five major histological types of ovarian carcinomas

	HGSC	LGSC	MC	CCC	EC
Mean age	61	55	56	57	56
Frequency	69 %	4 %	3 %	11 %	10 %
Stage at diagnosis	III/IV	III/IV	I	I	I
Risk factor	Ovulation	?	Smoking	Endometriosis	Endometriosis
High-penetrance genes	BRCA1/2	?		Lynch syndrome	Lynch Syndrome
Susceptibility loci	9p22.2, 2q31, 8q24	?	TYMS		
Response to chemotherapy	Good	Poor	Poor	Poor	Unknown
Cell lineage markers	WT1	WT1	TFF3	HNF1B	PR, VIM
Molecular alterations	TP53, BRCA1/2	KRAS	KRAS, ERBB2	ARID1A PI3K	ARID1A PTEN CTNNB1
New targeted therapies	PARP	MEK inhibitor	Trastuzumab	Temsirolimus	?
Survival in stage Ia	NA	>95 %	>95 %	~90 %	>95 %
Survival time in stage III	~36–60 months	60–80 months	20 months	20 months	?
Molecular subtypes	C1–C5	?	?	?	?

HGSC high-grade serous carcinoma, *LGSC* low-grade serous carcinoma, *MC* mucinous carcinoma, *CCC* clear cell carcinoma, *EC* endometrioid carcinoma

clinical behavior. They arise from well-characterized precursor lesions, most notably endometriosis and atypical proliferative (borderline) tumors, and are comprised by endometrioid, mucinous, and low-grade serous carcinoma, and probably most clear cell carcinomas. Type II tumors appear to progress rapidly and account for the vast majority of ovarian cancer deaths. These are typically high-grade serous carcinomas and its variants including carcinosarcomas and undifferentiated carcinomas. Although their origin is not completely resolved, accumulating data strongly suggest an origin from intraepithelial carcinoma of the fallopian tube. Indeed, some investigators believe that "the evidence supporting the fallopian tube as the site of origin of the most common type of ovarian cancer is indisputable" [15]. In the current report, the two viewpoints are compared and contrasted. They are not mutually exclusive; rather, they complement one another in evaluating our current understanding of ovarian carcinomas. These views have important implications for screening, diagnosis, and treatment, which are discussed later in this chapter.

Histological Type

It has long been noted that histological types of ovarian carcinomas are phenotypically quite heterogeneous at the microscopic level, in contrast to other cancer sites such as colon or breast. Eight histological types were accepted for the first WHO classification in 1973 and the current WHO classification system changed only slightly [16]. With the upcoming new edition, further modifications can be anticipated. The recognition of a morphologically distinct subset of serous carcinomas associated with oncogenic alterations in the MAPK pathway will single out low-grade serous carcinomas from the conventional high-grade serous carcinomas [14, 17–19]. Transitional cell carcinoma and undifferentiated carcinoma show morphologic and molecular alterations most consistent with serous carcinoma and will likely be incorporated into this group [20, 21].

Reproducibility

A cell type-specific management would be the logical consequence of the above data, but the lack of reproducibility for cell type diagnosis has hindered progress. Historically, the reproducibility of ovarian carcinoma cell type diagnosis has been reported as only modest. In a recent abstract, Patel et al. reported substantial interobserver agreement (kappa = 0.67) for histological type among gynecological pathologists but only moderate agreement (kappa = 0.54) among general pathologists using the current WHO classification [22]. With refined criteria and limiting the number of histological types to the five major types (high-grade serous, clear cell, endometrioid, mucinous, low-grade serous), reproducibility is now excellent among pathologists (kappa = 0.89) after being trained to apply new thresholds [23]. Similarly, Malpica et al. reported excellent interobserver agreement for the distinction of low-grade versus high-grade serous carcinomas [24, 25]. If patient management is going to be type specific, correct classification is fundamental. Further studies are needed to validate whether robust diagnosis can be expected in general pathology practice and to assess the value of ancillary molecular techniques such as immunohistochemistry to enhance reproducibility.

Immunohistochemical markers are generally expressed in a cell lineage-specific manner. The most useful markers are WT1 and HNF1B which, in combination with ER, reliably

allow the distinction of high-grade serous from clear cell carcinomas [26]. We recently developed a 9-marker immunohistochemical classifier which showed kappa 0.85 agreements in the validation cohort with the gold standard of histological type [20]. This marker panel was externally validated using clinical trial material with 90 % agreement with type [27]. These exercises show that immunohistochemical markers can be used to support histological type diagnosis in cases with ambiguous morphology or even for confirmation in straightforward cases. Further interlaboratory quality assurance is needed to ascertain that test performance is comparable among pathology laboratories.

Concomitant with improvement in cell type classification, the frequencies for certain type diagnoses have changed, in some instances, dramatically. The combined data from a hospital-based and population-based review of more than 2,000 consecutive cases [28] indicate major diagnostic shifts. The frequency of mucinous carcinomas has changed from a former mean of 12 % and a high of nearly 20 % to now consistently around 3 % with the increasing recognition and exclusion of metastatic mucinous carcinomas mainly from the gastrointestinal tract [29–32]. Endometrioid carcinomas now account for only 10 % of cases due to the recognition that gland-forming carcinomas with high-grade nuclear atypia, but expression of the serous cell lineage marker WT1 should rather be considered as high-grade serous carcinomas [21, 33].

Screening

A common statement in the ovarian cancer literature is that ovarian cancer presents with advanced disease, which makes complete resection impossible and reduces survival times from >90 % in stage I to ~30 % in stage III/IV disease. Based on these data, there is a general claim of a need for early detection in order to reduce mortality. However, the basis of this assumption is flawed. Namely, the disease that is diagnosed in stage I is fundamentally different from that diagnosed in stage III. That is, "advanced ovarian cancer" is distinct from localized or "early ovarian cancer." The difference is not at all a matter of progression over time but rather of underlying biology from the get-go. Almost 90 % of advanced ovarian cancers are high-grade serous carcinomas, the cell type which comprises a minority in "early-stage" disease. Low-stage or localized tumors are endometrioid, mucinous, or clear cell carcinomas usually presenting as a comparatively large pelvic cystic mass and are confined to the ovary or pelvis at the time of diagnosis (stages I and II). Women diagnosed with those tumors have an excellent outcome [34, 35]. High-grade serous carcinomas, on the other hand, carry molecular alterations that render these tumors more aggressive and are almost never diagnosed when confined to the ovary [28].

Results from many studies including a large ($n > 200{,}000$) screening study (UKCTOCS) showed that the majority of cancers detected by screening were serous in high stage, suggesting that current approaches fail to detect high-grade serous carcinomas in low stage [36]. A multimodal conventional screen of 241 women with *BRCA1/2* germ line mutations failed miserably to detect early high-grade serous carcinomas (HGSC) even in this high-risk cohort [37]. Most notably, the ovarian cancer screening arm of the ongoing PLCO trial was recently stopped due to a clear failure to reduce mortality after a median of 12.4 years of patient follow-up [38]. It is also important to recognize that screening for ovarian cancer is not without risk. Screening generates surgical procedures in a significant minority of women, the vast majority of whom do not have cancer. In the PLCO trial, the risk of serious complications of surgical procedures that would not have been undertaken was significant [38]. Current approaches such as transvaginal ultrasound, which focus on the ovary, predominantly detect benign tumors or indolent carcinomas of endometrioid, mucinous, or clear cell type.

Hence, new approaches are needed to detect HGSC. Over the last decade, a previously recognized but ignored precursor lesion for HGSC has been identified in the distal fallopian tube [3, 4, 9, 39–42]. This precursor is termed serous tubal intraepithelial carcinoma (STIC) and is thought to give rise to an ovarian tumor by implantation of metastatic tumor cells dislodged or exfoliated from the fallopian tube. This shift in understanding about the site of origin explains why HGSC are almost never diagnosed confined to the ovary. They seem to possess immediate access to the peritoneal cavity and are equipped with the most aggressive molecular alterations that result in high proliferation. Brown and Palmer modeled the occult phase of HGSC [43]. They concluded for HGSC that the window of opportunity for early detection lasts about 4 years, that tumors during that time period are less than 1 cm, and that "to achieve a 50 % reduction in serous ovarian cancer mortality with an annual screen, a test would need to detect tumors of 0.5 cm in diameter" [43]. Thus, formidable challenges are to be overcome. The small tumor size required for early detection means that biomarker assays need to be ultrasensitive but also specific. Biomarkers have to be selected for the tumor type of interest since biomarker expression across types is heterogeneous [1]. Imaging techniques have to be rethought. At least now we know where to search. Possibly, endoscopic techniques coupled with fluorescent dyes as used in other organs systems may help in screening of certain high-risk cohorts [44].

Risk-reduction strategies will theoretically now shift toward pure salpingectomy with preservation of the ovaries and hormonal function [45], and there are now efforts to encourage bilateral salpingectomy at the time of

hysterectomy when the ovaries are being retained [15]. On the other hand, current screening approaches, which typically detect low-risk lesions, need to be revisited. Risk models as to when commence surgery versus observation need further development [37].

Classification of Tumor Site Versus Type

There is a traditional fixation on tumor site as the primary discriminator in classification systems, which dictates subsequent patient management. Serous carcinomas have been traditionally classified as of ovarian, peritoneal, or fallopian tube origin, based on the largest tumor mass or by exclusion, i.e., with less than 5 mm of ovarian involvement and no fallopian tube involvement, the tumor has been classified as peritoneal. Jarboe et al. demonstrated how arbitrary such an approach is [46]. They showed that HGSC in symptomatic women were classified as ovarian 90 % of the time but in asymptomatic women with *BRCA1/2* germ line mutation as fallopian tubal 100 % of the time. There is a very clear bias in assigning the primary site to the ovary when the site of origin of an extrauterine high-grade serous carcinoma is uncertain. This clearly shows the limitations of a rigid site-specific classification system. Current synoptic reporting schemas for pathology reports differ between ovarian, peritoneal, and fallopian tube carcinomas causing diagnostic and staging confusion, i.e., an HGSC with a predominant tumor mass in the ovary and a STIC may be traditionally classified as ovarian carcinoma with fallopian tube involvement or as STIC metastatic to the ovary. For advanced HGSC, primary site assignment is often arbitrary. It is time to think about a disease-specific classification system.

Classification of Tumor Type Versus Grade

Traditionally, grading has been used to describe the biology of ovarian carcinomas. Several grading systems have been used. The WHO promoted a universal grading system developed by Silverberg and coworkers [47]. Despite repeatedly showing significant prognostic stratification [48], it had not until recently been scrutinized for interobserver reproducibility. Several studies showed that grading had inferior reproducibility compared to histological typing [49, 50]. Furthermore, the grade 2 or moderately differentiated category comprises a very heterogeneous group of less-aggressive mucinous and endometrioid carcinomas together with grade 2 serous carcinomas that are prognostically indistinguishable from grade 3 serous carcinomas [51]. There is now a move toward type-specific grading systems [25]. Binary grading parameters reproducibly distinguish the two types of serous carcinomas: low-grade and high-grade serous [24], which have markedly differing survival rates [52]. The FIGO grading system may be used in endometrioid carcinomas in analogy to endometrial carcinomas [25]. No established grading systems exist for mucinous and clear cell carcinomas, although there have been recent efforts to define a grading system for clear cell carcinoma [53]. Molecular markers will have likely a greater potential to delineate subgroups within histological types as demonstrated for high-grade serous carcinomas [54, 55].

Type I Versus Type II Pathogenetic Categories

A recent correlation of morphologic and molecular biological data has led to the proposal of a new model of pathogenesis of ovarian carcinoma [14]. The combination of morphology with stage distribution, molecular biological features, and clinical behavior suggests that there are two fundamentally different types of ovarian carcinomas. It should be emphasized that this is not a proposal for any change in terminology; it is, rather, a dualistic model of pathogenesis and biology and is entirely compatible with the cell type classification discussed earlier in this chapter.

When viewing the clinical and pathological features of all ovarian carcinomas as a group, there is a stark anomaly that is immediately apparent. Stage I ovarian carcinomas, those confined to the ovaries and therefore considered "early ovarian carcinomas," are significantly larger as compared to the primary ovarian tumors in advanced-stage carcinomas which are disseminated throughout the peritoneal cavity. Several groups have shown that stage I ovarian cancers average 15 cm, while the ovarian tumors in stage III are 10 cm in diameter [56]. How could this be? How could "tumor progression" to a more advanced, or "later," stage be associated with a reduction in tumor size? Do tumors shrink as they progress and become more aggressive?

Further evaluation reveals other differences. Stage I tumors have an overwhelming tendency to be non-serous and are usually clear cell, mucinous, and endometrioid, while stage III and IV tumors are typically high-grade serous [19, 28, 57]. This finding of differences in stage distribution goes a long way toward explaining the apparent temporal anomaly. For it now becomes clear that we are looking at entirely different tumors. Endometrioid, mucinous, and clear cell carcinomas tend to present in low stage and are characterized by large tumor size. High-grade serous carcinomas nearly always present in stages III and IV and the primary pelvic tumors are smaller. It is thereby resolved that stage I tumors do not violate the laws of physics or biology by shrinking as they progress. In the vast majority of cases, stage I and stage III/IV ovarian cancers are different diseases characterized by different cell types and accordingly differing molecular biological, clinical, and behavioral

features. The clinical importance of these differences is highlighted by the fact that 90 % of ovarian cancer deaths occur in women with high-grade serous carcinomas, i.e., type II tumors, while type I tumors are quite indolent, are cured in a majority of cases, and account for only about 10 % of ovarian cancer deaths.

Type I tumors are biologically low-grade neoplasms. Morphologic and molecular data indicate that they arise from atypical proliferative (borderline) tumors and endometriosis. They have a long natural history and usually present as large stage I neoplasms [35]. The type I group includes low-grade serous carcinoma (invasive micropapillary serous carcinoma), low-grade endometrioid and mucinous carcinoma, and probably most clear cell carcinomas. Although clear cell carcinomas exhibit most of the features of type I tumors including presentation in stage I and association with a well-established precursor lesion (endometriosis), it is typically high grade unlike the other type I tumors and may have a worse prognosis. Nonetheless, molecular data show a greater similarity of clear cell carcinoma to type I rather than type II tumors. Type I tumors usually contain somatic mutations of genes encoding protein kinases including *KRAS*, *BRAF*, *PIK3CA*, and *ERBB2*, as well as other signaling molecules including *PTEN* and *CTNNB1* (beta-catenin) [9].

Endometrioid carcinomas typically arise from endometriosis. Although the literature suggests that only one-third to one-half of endometrioid carcinomas are associated with endometriosis, recent improvements in cell type classification have clarified the important distinction of high-grade endometrioid carcinoma from high-grade serous carcinoma. When this distinction is properly made, many high-grade predominantly glandular adenocarcinomas that were previously classified as endometrioid, and were not generally associated with endometriosis, are now recognized as serous. Accordingly, when true endometrioid carcinomas are evaluated, the association with endometriosis is much stronger, and in our experience, the vast majority of true endometrioid carcinomas arises in association with endometriosis [19]. Examination of the morphology of endometrioid carcinomas reveals a spectrum of proliferation with the frequent presence of an atypical proliferative/borderline component, like the other type I tumors.

Mucinous carcinomas are the largest in size of ovarian tumors. They also display morphologic heterogeneity with a characteristic spectrum of proliferation. A typical ovarian mucinous carcinoma contains many areas of benign mucinous cystadenoma and more proliferative areas of atypical proliferative/borderline mucinous tumor. In most cases, confluent or destructive glandular proliferation warranting a diagnosis of invasive carcinoma comprises only a minority of the tumorous mass. These findings fit with the characteristic type I tumor pathogenetic model indicating an origin in benign mucinous cystadenomas analogous to the origin of clear cell and endometrioid carcinomas from endometriosis.

Low-grade serous carcinomas arise from atypical proliferative serous tumors (APST; serous borderline tumors). Like the other type I tumors, they display a morphologically intermediate form. For these tumors, the morphologic features of microinvasion, microinvasive carcinoma, and/or noninvasive micropapillary serous carcinoma (MPSC) are present in most cases concomitant with larger areas of invasion, warranting a diagnosis of invasive low-grade serous carcinoma. Unlike other type I tumors, however, they do not often present in stage I. This would appear to be due to their frequently exophytic architecture and association with so-called peritoneal implants, which may be invasive or noninvasive, allowing these tumors to involve the peritoneal surfaces even prior to displaying enough invasion for an outright diagnosis of carcinoma.

Inasmuch as type I tumors usually present in stage I, they are indolent and have an excellent prognosis. Most studies show that comprehensively staged stage I ovarian carcinomas are associated with survival rates exceeding 90 % [34, 35]. The justification for the development of a screening test has been this high cure rate for "early-stage" ovarian cancers. What is lacking in allegedly encouraging reports of screening studies, however, is an appreciation that these are not early versions of most fatal ovarian cancers. Ovarian cancer fatalities are overwhelmingly due to type II tumors, i.e., high-grade serous carcinomas. Screening studies often claim potential success when they identify large stage I tumors; however, what is not understood by these investigators is that this group is the wrong target for such a screening test if a reduction in ovarian cancer mortality is the goal.

High-grade serous carcinoma is by far the most common type of ovarian cancer. These have been considered to be aggressive high-grade neoplasms from the outset. In the past, they have been thought to arise "de novo." However, it must be acknowledged that nothing comes from nothing, as pointed out by both philosophers and singer-songwriters. As discussed earlier, it now appears likely that most high-grade serous carcinomas arise from the mucosa of the fallopian tube. These tumors and their putative precursor, STIC, are characterized by *TP53* mutations. STICs have been identified most often in the tubal fimbriae and have been shown to have the same *TP53* mutations as the associated carcinomatosis [39, 40]. It therefore appears that at the morphologic and molecular level, early- and advanced-stage high-grade serous carcinomas are very similar.

The identification of the tubal origin of these tumors explains many previously inexplicable facts about high-grade "ovarian serous carcinomas" including the rarity of stage I and II tumors, the failure to identify a viable precursor lesion in high-risk ovaries, and the apparent rapidity of peritoneal dissemination. The location of the noninvasive

precursor in the tubal mucosa where it is exposed to the peritoneal cavity and can exfoliate and implant on the peritoneum even prior to displaying morphologically invasive properties solves the conundrum of why these tumors do not remain localized in the pelvis long enough for screening tests to identify them.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is becoming an alternative option for advanced ovarian cancer based on a recent clinical trial [58]. The decision to commence neoadjuvant chemotherapy is still mostly based on clinical grounds and cytology [59]. Although nearly 90 % of advanced-stage ovarian carcinomas will be high-grade serous carcinoma or its variants, there is a small fraction of other types, which are resistant to chemotherapy [60–62]. For example, low-grade serous carcinomas, although uncommon, comprise 6–9 % of high-stage ovarian carcinomas. Upfront surgery without prior chemotherapy would be the desirable approach to low-grade serous carcinoma. To that end, core biopsies or ascitic fluid may be of great value before triaging women to neoadjuvant chemotherapy or upfront surgery. Core biopsies or cell blocks generally obtain a sufficient amount of tissue for a robust cell type diagnosis with the use of immunohistochemical markers in difficult cases [26]. A recent study showed that response to chemotherapy cannot be predicted by histological features of HGSC [63].

Extent of Surgery/Necessity of Staging

It is traditionally believed that surgical staging and debulking is the cornerstone in ovarian carcinoma management. The historic role of staging and debulking includes (1) to inform on adjuvant treatment and (2) to improve recurrence and survival rates. Treatment guidelines are stage based. The staging system categorizes the extent of disease. To date, administration of adjuvant therapy is mainly based on the extent of the disease with only limited recognition of the unique biology of the different cell types. Although biology and extent are highly correlated, e.g., high-grade serous carcinoma is widespread at diagnosis, there are biologically less-aggressive tumors with extensive disease and there are aggressive tumors with limited disease. It seems that there are meticulous efforts in place to assess the extent via staging, but the assessment of biology needs improvement.

Historically, grading and histological type were plagued by poor reproducibility. Molecular markers are promising but they need to be considered in the right context [1]. To date, refined histological type seems to be reproducible and to best reflect known molecular alterations [23]. It is worthwhile to consider the advantages of a type-specific management of ovarian carcinomas. We have recently shown that endometrioid and mucinous carcinomas diagnosed in stage Ia/Ib, with or without chemotherapy, had an excellent outcome with over 95 % disease-specific survival [34]. Notably, these patients were treated at centers where comprehensive staging was not part of standard care. Hence, these outcomes are based on demonstrating a less-aggressive biology and apparent extent. On the other hand, high-grade serous carcinoma diagnosed at stage I/II had an unfavorable outcome with a 57 % 10-year survival rate even though almost all patients were treated with adjuvant chemotherapy. Other groups have shown similar findings [35]. The argument to be made here is that biology is the driving force of the tumor and extent is only a comparatively poor surrogate.

Unanswered questions remain: (1) Why should less-aggressive tumors be aggressively staged? For example, in the typical scenario of a pelvic cystic mass, surgery is performed without upfront diagnosis. Intraoperative consultation with frozen section shows a mucinous neoplasm with some confluence. The differential diagnosis is atypical proliferative (borderline) mucinous tumor versus mucinous carcinoma. Such a case would almost certainly get comprehensive staining at most institutions although the chances of finding occult extraovarian disease are slim [64]. (2) Why comprehensively restage a low-volume high-grade serous carcinoma? For example, an ovarian mass was removed without intraoperative consultation and final pathology is high-grade serous carcinoma. Such a case would almost invariably be taken back to the operating room for a completion staging surgery with a high probability of additional disease detected. But does this second surgery change the management other than delaying adjuvant chemotherapy? The concept of surgical cure of disseminated cancer is a weak one (albeit less-aggressive cancers can be controlled and salvaged by surgery over long periods).

Choice of Adjuvant Treatment

High-grade serous carcinomas are exceedingly rare in stage Ia. Stage I and II high-grade serous carcinomas have a 10-year cancer-specific survival of 57 % [34]. This would justify the need of adjuvant chemotherapy for high-grade serous carcinoma based on biology irrespective of stage because there is no subset with favorable outcome, the only possible exception being the morphologically noninvasive precursor, STIC [65]. This viewpoint is in clear contrast to the conclusions of highly influential trials such as the ACTION trial [66, 67]. The conclusions are (1) that women with complete surgical staging had a better outcome, which could be explained by stage migration (“Will Rogers

phenomenon"), (2) that the "benefit from adjuvant chemotherapy appeared to be restricted to patients with nonoptimal surgical staging" or in other words that chemotherapy is not effective in optimally staged patients. However, given our knowledge that non-serous carcinoma is unlikely high stage and shows lower response to chemotherapy, one thinks on how contemporary histological type could confound those results. The hypothesis being that in the suboptimally staged "early"-stage ovarian cancers the outcome differences between observation and adjuvant chemotherapy are mainly driven by high-grade serous carcinomas. While the optimally staged group that showed no benefit from adjuvant chemotherapy is biased toward endometrioid, mucinous, and clear cell carcinomas, which show low response rates to chemotherapy anyway. For advanced-stage disease (almost 90 % are high-grade serous carcinomas), a recent clinical trial from Japan showed that dose-dense paclitaxel in combination with standard carboplatin improved the median progression-free survival from 17 to 28 months when compared to conventional administration of carboplatin/paclitaxel [68]. Poly(ADP-ribose) polymerase (PARP) inhibitor is a promising synthetic lethal compound in tumors with double-stranded break repair defects such as high-grade serous carcinoma [55]. Interestingly, a recent study showed response not only in *BRCA1/2* mutated HGSC but also HGSC without known mutation in 21 % of cases [69].

High-stage clear cell or mucinous carcinomas have an even more unfavorable outcome compared to high-grade serous carcinoma, likely due to the fact that if curative surgery is not possible, no effective adjuvant treatment is available [32, 61, 62, 70]. For clear cell carcinoma, radiotherapy is reconsidered as an option [71]. Because of similarities of mucinous carcinomas to colorectal carcinomas, colorectal chemotherapy regimens that contain 5-FU are being tested for mucinous ovarian carcinomas (mEOC/GOG241). However, colorectal carcinomas of mucinous type do respond less to standard treatment for 5-FU compared to usual colorectal carcinoma; it remains to be seen whether an empiric crossover of molecularly unrelated entities (i.e., colorectal carcinomas with APC pathway alterations compared to ovarian mucinous carcinomas with *KRAS* mutations) will be successful [62]. The quest for new therapies for special cancer types will need molecular groundwork.

New Targeted Therapies

Examples of possible new therapies include a recently launched National Cancer Institute of Canada (NCIC) IND.206 trial including ovarian clear cell carcinomas treated with sunitinib and temsirolimus. The latter is based on the high frequency of *PIK3CA* mutations in ovarian clear cell carcinomas with putative downstream activation of the mTOR pathway [72]. Mucinous carcinomas show *ERBB2* amplification in about 18 % of cases that can be targeted with trastuzumab [73, 74]. Mucinous and low-grade serous carcinomas both show a high frequency of *KRAS* mutations that could be targeted with some form of downstream MAPK inhibition.

Genetic Counseling

Studies have shown that hereditary mutations of *BRCA1/BRCA2* are restricted to patients with high-grade serous carcinomas [21, 41, 75]. Hence, in several Canadian provinces, a diagnosis of high-grade serous carcinoma triggers genetic counseling to investigate for an underlying germ line mutation. Endometrioid and clear cell carcinomas in a certain context (young age, family history, tumor morphology) may raise a suspicion of underlying Lynch syndrome, which can be followed up with the appropriate molecular test [76].

Conclusion

While the current management of ovarian carcinoma is very much centered around stage, future management will rely more on biology of the disease. A first step in subcategorizing ovarian carcinomas has been accomplished by including molecular information and refining cell type classification. The newly modified classification consists of five major histological types, which differ with respect to molecular alterations, clinical presentations, and response to therapy. Reproducible diagnosis of these five types can be made by morphology in combination with immunohistochemistry in >95 % of cases. We would advocate the use of good diagnostic markers either to confirm the morphologic diagnosis or to establish the histological type in ambiguous cases. This classification still relies on morphology, but due to strong phenotype–genotype correlations, morphology still provides a robust framework for the myriad interactions that occur at the molecular level that will require further approaches as systems biology. With disruptive technology advancing, we will gain a more comprehensive understanding of ovarian carcinoma types and discover new biomarkers for diagnosis and treatment. A body of work in order to biologically and technically validate those biomarkers lies in front of us. But we are convinced that H&E morphology will retain its value in the future in triaging specimens to the appropriate molecular test and help in the interpretation of molecular findings in the appropriate context (many mutations span over several histological types) or unusual findings (supersensitive next generation sequencing in which 2 % of the tumor cell population is positive for a certain mutation).

A comprehensive understanding of the biology of ovarian cancer embraces clinical course, morphologic features, and molecular alterations. The type I/type II dualistic model provides a framework consistent with the cell type approach. Since the vast majority of ovarian cancer deaths occur in women with type II tumors, this model informs efforts to delineate the appropriate target groups for screening, novel and aggressive treatment approaches, and ultimately prevention. These concepts will undoubtedly continue to evolve, particularly as more is learned about the likely source of most "ovarian cancers." The increasing recognition that the fallopian tube is the ultimate source of most fatal ovarian cancers is a critical conceptual advance that ultimately will lead to better screening and prevention strategies.

Concluding Comments

- Reproducible, biomarker-assisted subclassification of ovarian carcinoma is the mainstay for further progress in translational research and clinical management.
- Recognition of histological types as distinct entities should influence clinical trial design.
- Integration of standardized diagnostic algorithms regarding histological typing into pathology laboratories is a great challenge.

Disclaimer Dr. Seidman's contribution to this work is unrelated to his employment at the FDA. The opinions and assertions herein are the private views of the authors and are not to be construed as official nor as reflecting the view of the FDA or any other department of the US government.

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Lymphadenectomy in Endometrial Cancer: The Controversy Rages Unabated

4

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Summary Points

- There is agreement that lymphadenectomy is not warranted in low-risk endometrial cancer.
- There is continuing disagreement as to whether lymphadenectomy is clinically effective in high risk.
- The resulting differences in practice are unsatisfactory.

Introduction

Endometrial cancer is now the most common gynecologic malignancy in the USA, the UK, and Western Europe. In 2012, it is estimated that 47,130 women will be diagnosed with endometrial cancer in the USA and 8,010 will die of their disease [1]. The rising incidence of endometrial cancer and the increasing number of deaths are causes for concern and reflect the rising tide of obesity which has swept across much of the industrialized world over the past 20 years. The prevalence of obesity among adult women is now as high as 35.5 % in the USA [2]. Endometrial cancer is strongly associated with obesity, with an increased relative risk of 1.60 for each increment of body mass index (BMI) of 5 kg/m^2 over a threshold of 25 kg/m^2 [3]. Not only has morbid obesity brought greatly increased risk of endometrial cancer to women, it also presents challenges in ensuring that optimal therapy is delivered to patients who have multiple comorbidities. Despite this, endometrial cancer continues to be associated with a lower death rate than most solid tumors, due largely to its early presentation following postmenopausal bleeding. There are considered to be two kinds of endometrial cancer, endometrioid which is associated with obesity and other histotypes such as clear cell and serous, which are not. The non-endometrioid tumors carry a higher risk of death; indeed around 80 % of deaths occur in the 20 % of women with high-risk disease. "High-risk" factors include non-endometrioid histotypes, and within the endometrioid group are poorly differentiated (G3) and deeply myoinvasive tumors. Lymphovascular space involvement represents another important risk factor. Patients with "high-risk" disease are associated with increased probability of lymph node metastases, recurrence of disease, and death. Patients with lymph node metastasis have a poorer prognosis when compared to patients with negative nodes. FIGO staging guidelines governing endometrial cancer rely on surgical findings, including the lymph node status of the pelvic and para-aortic chains. These staging recommendations not only confer prognosis, they may also be used to determine the use of adjuvant therapy.

The backbone of treatment for endometrial cancer is total hysterectomy and bilateral salpingo-oophorectomy, which is increasingly being offered as a laparoscopic or robotic procedure. The major controversy in surgical treatment has been and continues to be the role of lymphadenectomy. Notwithstanding the prognostic value of the information provided by comprehensive FIGO staging, there has been considerable debate regarding its value to the patient with respect to tailoring of adjuvant therapy and survival. FIGO rules incorporate the pelvic and para-aortic lymph node status in determining the stage of disease; however, uniform surgical standards are not well defined. American guidelines emphasize the importance of surgical staging by reporting on a population of over 7,000 women with an overall 5-year survival for clinical stage 1 disease of 51 % compared to an 88 % survival rate when

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surgically stage 1 [4]. Patients can be inaccurately staged clinically, for example, clinical stage 1 is diagnosed in 59 % of women presenting initially and surgical stage 1 in 72 %, thus resulting in possible undertreatment [5]. There is also debate about what is meant by lymphadenectomy. The importance of complete surgical staging is to exclude the presence of occult disease (FIGO). The Gynecologic Oncology Group (GOG) surgical procedures manual describes staging of gynecologic malignancy nonspecifically with options of pelvic and para-aortic lymph node sampling and/or lymphadenectomy and/or high para-aortic lymphadenectomy to the insertion of the ovarian veins [6]. Some insist on a dissection from the distal end of the iliac chains up to the renal vessels, while others merely sample enlarged or suspect nodes, and many remain doubtful about the value of lymphadenectomy at all. The debate around lymphadenectomy forms the core of this chapter, in which both sides of the argument will be put, and then a possible way forward through the impasse that has developed.

The Case for Lymphadenectomy ("Mayo School")

Controversy regarding lymphadenectomy in endometrial cancer management has resulted in over a decade of debate and research in an attempt to improve survival and therapeutic benefit. Fortunately, among all patients at initial presentation lymph node metastasis is uncommon, ranging from 4 to 15 % [5, 7]. Disease recurrence, however, occurring in the pelvic or lymphatic areas, is highly lethal resulting in a survival rate of only 8 % in patients after no lymphadenectomy [8]. In the subset of women at high risk of nodal dissemination, it seems essential to evacuate lymphatic tissue in an effort to reduce lethal recurrence risk. High-risk patients undergoing complete lymphadenectomy with stage 1 disease do not require adjuvant therapy to ensure recurrence rates of less than 10 % and an overall survival higher than 80 % [9], thus decreasing the morbidity associated with undue adjuvant radiation and chemotherapy. In contrast, high-risk patients without lymphadenectomy and apparent stage 1 disease treated with pelvic radiotherapy experience higher recurrence rates up to 31 % distantly and 14 % locoregionally and a lower overall survival rates of 58 % [10]. This suggests that without lymphadenectomy, women are inappropriately classified and possibly undertreated.

The time has come for a call to arms toward determining factors important in directing selection of patients at sufficient risk for lymphatic metastasis who may benefit from complete pelvic and para-aortic lymphadenectomy. As we identify this important at-risk subset of women, we gather the troops if you will, whereby we may then appropriately stage with systematic lymphadenectomy in an effort to map the battlefield of disease dissemination, paving the way for adjuvant treatment to directly attack this potentially lethal cancer.

Assembly of the Troops

Correctly identifying at-risk patients may decrease the surgical morbidity of unnecessary lymphadenectomy and avoid over- or under-prescribed adjuvant treatment. It is generally agreed upon that low-risk patients with minimal myometrial invasion and grade 1 lesions do not require lymphadenectomy. These patients display 5-year rates of recurrence of 5 % or less without lymphadenectomy or adjuvant radiation [10, 11]. Previous trials investigating lymphadenectomy have included low-risk diluted populations, with grade 3 lesions making up only 22–33 % of those studied [12, 13].

Determining a set of reliable tumor factors to aid in the selection of those patients at risk for lymphatic metastasis that may benefit from systematic lymphadenectomy is the charge. These factors may be preoperative factors or, better, intraoperative frozen section, if available and accurate. Reports from preoperative biopsy or intraoperative frozen section findings are not always reliable and frequently change upon final pathology report. Preoperative biopsy grade is upgraded in the surgical specimen in 1 in every 6 patients [14]. Blinded evaluation of endometrial cancer frozen section specimens has been reported to ultimately be upgraded or upstaged 28–44 % of the time on final pathology. The accuracy of correlation with final pathology is improved with deeper invasion and grade 3 pathologies [15]. Other preoperative risk factors for selection have been analyzed and determined that MRI tumor volume index and serum CA-125 levels may predict pelvic and para-aortic metastasis [16]. A strategy to circumvent postoperative changes could incorporate several features altogether.

A prospective Mayo Clinic study utilized an algorithm based on intraoperative uterine factors to determine which patients needed a lymphadenectomy thus selecting an at-risk population of patients with 22 % harboring positive nodes. The uterine factors used to indicate lymphadenectomy were primary tumor diameter greater than or equal to 2 cm, grade 3 or non-endometrioid histology, and/or myoinvasion greater than 50 %. Furthermore, among low-risk patients with tumor diameter less than or equal to 2 cm, grade 1–2 endometrioid histology, and less than 50 % myoinvasion, a negligible probability (<1 %) of lymph node metastases or lymphatic recurrences is observed [17, 18]. We acknowledge that such institutional pathology services are not universally available; however, this algorithm is currently practiced at the Mayo Clinic [7, 17, 18]. More recently it has been proposed that combining preoperative histology, intraoperative tumor diameter, and the absence of gross extrauterine disease is accurate in the selection of low-risk patients as well, when frozen section is not available [19]. Selecting factors that do not result in a moving target would be ideal to accurately ascertain those patients who are most likely to benefit from staging. The window of opportunity to stage and provide inclusive

frontline treatment does not present twice, making it essential to optimize our resources at initial diagnosis. There will be inherent institutional variation in the resources available. Predictive patient selection is fraught with imperfection leaving the ideal set of variables a matter worth consideration.

Mapping of the Battlefield

Endometrial cancer is most often detected at early stages, and rates of lymph node metastasis in this setting are less common. The rate of nodal metastasis among clinically stage 1 women is 11–13 % [13, 20]. The most reliable way to map the presence of lymph node metastasis is to remove lymph tissue for complete histologic evaluation. Delineating the battlefield is important to employ a focused attack and eliminate unnecessary injury. Lymph node enlargement is not a reliable indicator of metastasis, and the literature has shown that metastatic pelvic and para-aortic nodes average 6.8–9 mm diameter [21]. One study showed that 37 % of the time, positive pelvic lymph nodes measure less than 2 mm in diameter [22]. Therefore, lymphadenectomy coincides with staging guidelines and serves as the most reliable method to identify occult disease.

The rate of nodal metastasis in patients with grade 1 disease and minimal myometrial invasion is low at 0–7 %, while those with grade 2–3 lesions or deep myometrial invasion have a 25–33 % risk for nodal metastasis [20, 23]. Lymph node metastasis demonstrates that the disease has spread beyond the uterus, serving as an indication for adjuvant therapy and aiding in projecting prognosis. The pelvic lymph nodes are the most common location for nodal metastasis, involved in 83–84 % of cases with lymphatic spread followed by para-aortic node metastasis in 62 %. The route of lymphatic spread in endometrial cancer is not always predictable. Negative pelvic nodes with positive para-aortic metastasis may be found in 16–17 % of patients with lymphatic spread and ovarian vein metastasis in 28 % of para-aortic node-positive cases [7, 24]. One study showed that the ipsilateral common iliac nodes were negative for disease in 71 % of patients with para-aortic metastasis and that gonadal vessel metastasis was only seen in the presence of para-aortic metastasis suggesting a preferential dissemination that bypasses the pelvic nodes. When para-aortic metastases are present, there is disease superior to the inferior mesenteric artery 77 % of the time [7]. This unpredictable pattern of spread strongly suggests that a focused pelvic lymphadenectomy would largely underestimate the true extent of disease. Neglecting to appreciate this phenomenon will result in suboptimal radiochemotherapy. Para-aortic lymphadenectomy to the level of the renal vessels is necessary to exclude occult disease.

Knowledge of lymph node metastasis significantly influences prognosis and thus patient management. There are retrospective data to suggest a therapeutic advantage after para-aortic lymphadenectomy. A Japanese review evaluated a cohort of 671 patients having pelvic or combined pelvic/para-aortic lymphadenectomy and found that the combined lymphadenectomy group's hazard ratio for death was 0.53 (p=0.0005) [25]. High- and intermediate-risk stratified patients had a statistically significant 10 % increase in overall survival. When treated similarly with chemotherapy, recurrence rates were 20 % less in the combined lymphadenectomy group, and aortic node recurrence following para-aortic lymphadenectomy was significantly less at 1.3 % versus 9.5 % [26]. Among 51 patients with metastatic nodal disease receiving equal amounts of radiotherapy, those having a systematic para-aortic lymphadenectomy had a significantly improved 5-year overall survival, 77 % versus 42 % [27]. Moreover, patients with positive para-aortic lymph nodes were without nodal recurrence when receiving an adequate lymphadenectomy and radiotherapy, compared to those receiving either inadequate lymphadenectomy or no radiotherapy having nodal recurrence from 34 to 69 % n=41 [28]. Conflicting definitions exist for "adequate" lymphadenectomy; nonetheless, a judicious dissection effort in future trials is needed.

The prospective studies that have been undertaken to define a possible therapeutic benefit of lymphadenectomy have contained populations at low risk undergoing a nonsystematic pelvic and para-aortic lymphadenectomy with low lymph node counts [12, 13]. The idea that performing solely a pelvic lymphadenectomy may result in a measurable therapeutic benefit does not seem reasonable, considering that node-positive patients harbor para-aortic metastasis 62–67 % of the time [7, 24]. Furthermore, performing a para-aortic lymphadenectomy to the level of the inferior mesenteric artery would miss 38–46 % of node-positive women with para-aortic metastasis. Therefore, it should come as no surprise that surgery and adjuvant treatment for the pelvis that ignores the para-aortic region, whether it be lymphadenectomy or radiotherapy, has not been shown to improve survival. A comparison made between pelvic and pelvic with para-aortic lymphadenectomy revealed no differences in lymphedema, secondary surgery, thrombosis, or blood transfusion despite an increase in mild to moderate ileus occurrence and operative time [26]. In the hands of a skilled gynecologic oncologist, complications between the two approaches are similar and certainly do not warrant exclusion of thorough staging.

Launching a Strategic Attack

Like many surgically managed cancers, the initial aim in endometrial cancer is to remove tumor burden and survey for occult disease. This knowledge serves to then tailor adjuvant therapy and surveillance. The battle against cancer becomes eloquently deliberate. Lymph node metastasis is an indication for more extensive adjuvant therapy. Numerous studies have shown promising overall survival rates for stage 3C1

and 3C2 patients treated with chemoradiotherapy (100 and 75 %, respectively) or, less successful, with chemotherapy alone (86 and 48 %) [29, 30]. Identifying these patients for adjuvant treatment is necessary to optimize long-term outcomes. Para-aortic metastasis targeted directly resulted in improved outcomes, and data showed that nodal recurrence rates of 0 % can be obtained with adequate lymphadenectomy and extended field radiation [27].

Pelvic external radiation therapy, when disease is confined to the uterus, has been shown to improve locoregional control, with no survival benefit. This observation has made its use controversial and a subject of debate [31, 32]. In disease that poses a reasonable risk of nodal dissemination, exploration is obligatory. Systematic lymphadenectomy to exclude advanced disease may omit the use of adjuvant chemoradiotherapy and associated morbidity. Women with intermediate-risk disease confined to the uterus, which is properly staged to exclude lymph node metastasis, have recurrence rates of less than 8 % without the use of adjuvant treatment [11].

Reflect on a hypothetical population of 100 clinically stage 1 women at high-intermediate risk for lymph node disease with 20 % of them harboring metastasis. Those receiving systematic staging would result in 20 node-positive women with focally directed adjuvant therapy and 80 women having received a negative lymphadenectomy. Conversely, 100 unstaged presumed stage 1 women would all receive pelvic radiotherapy based on uterine factors, resulting in 13 of 20 node-positive women being undertreated for their para-aortic metastasis and 80 women potentially overtreated with radiation. A patient would be 2.9 times more likely to receive correct treatment of lymph node metastasis when undergoing staging lymphadenectomy in this theoretical population [33]. Previous prospective trials have not only failed to exclude occult disease in an at-risk population but have also negated to consider lymph node status to direct postoperative treatment [12, 13].

In summary, this call to arms solicits further investigation to assemble those women at risk, precisely map their disease dissemination, and launch a directed therapeutic attack. We get one chance to do it right the first time and combat against an unjust lethal recurrence. Why holster the armament of lymphadenectomy when its use could offer a therapeutic advantage and better define the need and extent of adjuvant therapy and patient prognosis? "The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, union of forces is necessary" (W. J. Mayo).

The Case Against Lymphadenectomy ("Manchester School")

Lymphadenectomy could be performed solely for the purpose of surgical staging, because it was felt to be potentially therapeutic by removing metastatic disease, or because it would guide adjuvant therapy. There is little doubt that nodal metastases constitutes the most powerful prognostic factor, though a small proportion of node-negative women will develop recurrent disease. Lymph node metastases do not constitute the only prognostic factors; myoinvasion, tumor differentiation, lymphovascular space involvement, and spread to ovaries, cervix, and parametrium are all prognostic factors.

As previously stated, around 20 % of endometrial cancer cases constitute higher-risk disease, which is more likely to be associated with recurrence and death. It has been common practice in many centers in Europe to base adjuvant therapy on the profile of tumor characteristics to select adjuvant radiation and more recently chemotherapy. The use of adjuvant radiotherapy and its risk of treatment complications have become more restricted with the results of recent trials showing no impact in overall survival.

The Confusion

The main goal in surgery of endometrial cancer is to remove the primary tumor and to optimize the likelihood of cure. Surgery inevitably carries risk which is increased in older obese women with comorbidity, some or all of which frequently features in women with endometrial cancer. Surgery should avoid unnecessary risks, and as in all of medicine, the risk of benefit needs to be balanced against the risk of harm. Surgical findings, particularly histopathology, should form the basis for evidence-based adjuvant therapy, which is stratified according to the risk factors determined as a result of surgery.

Where does lymphadenectomy fit into this reasoned approach? It will not be part of removing primary tumor, but it may remove micrometastases in lymph nodes, which potentially could provide some direct therapeutic effect. In order to provide accurate FIGO staging, it requires a systematic dissection of the pelvic and para-aortic chains, which, according to the Mayo School, should extend to the renal vessels. This is not a trivial undertaking, and though in highly skilled hands may not cause a great deal of morbidity, it has in less skilled hands the potential to cause major hemorrhage and other morbidity. Furthermore, it consumes not inconsiderable healthcare resource in terms of theatre time, consumables (especially in laparoscopic/robotic surgery), and can result in lymphedema of the lower limbs, particularly if adjuvant radiation is performed. With regard to prognosis and the need for adjuvant therapy, the surgeon might well feel better equipped to manage the patient optimally by having staged the patient, as in "know the enemy."

There is a spectrum of opinion on the value of lymphadenectomy. On one wing of the debate are those who feel that maximal node retrieval can improve the patient's prospects, if not by direct therapeutic effect, by tailoring the selection of adjuvant therapy, and in node-negative women the

avoidance of adjuvant therapy. On the other wing are those who feel lymphadenectomy is a waste of time, effort, and expense because it cannot exactly tailor adjuvant therapy as this is required for node-negative women deemed to be at high risk by virtue of well-recognized tumor characteristics, such as grade, myoinvasion, and LVSI.

So, how did we come to a confused situation like this, and what is the evidence base?

The Evidence Base

The original evidence put forward by protagonists of lymphadenectomy was a series of studies using the US SEER database, which allows individual survival to be analyzed with reference to tumor risk factors, including number of lymph nodes removed. Several of these studies revealed an association between more extensive lymph node dissection (grouped by numbers of nodes removed) and better survival. In one of these studies [34], the reported data showed an implausible difference in survival in node-positive women from around 50 % at 5 years to 70 % depending on whether fewer than 10 nodes or more than 20 nodes were removed. Another study [35] showed that cardiac specific death was less likely in women undergoing lymphadenectomy, which appears to have no biological plausibility. What these case control studies demonstrate are associations, not causal relationships, because behind the data are many possible confounding factors including the overall quality of the entire management package and more morbid frail women who are likely to die sooner from any cause undergoing more limited lymphadenectomy.

There was an obvious need for a randomized trial to resolve this uncertainty and after no such trials, like buses, along came two in rapid succession! These trials differed somewhat in design, in terms of adjuvant therapy, but both involved a primary randomization to lymphadenectomy or no lymphadenectomy for endometrial cancer thought to be confined to the uterus. They were reported within 2 months of each other in 2008/2009.

The UK ASTEC trial [12] randomized all stage I endometrial cancer to pelvic lymphadenectomy or no lymphadenectomy though excision of an enlarged node was permitted if the surgeon felt that was in the woman's best interest. Thereafter, higher-risk women, irrespective of nodal status, were re-randomized to adjuvant radiation or no radiation. In the Italian trial (no acronym) [13], women were again randomized to lymphadenectomy, but para-aortic dissection was allowed, and women received adjuvant therapy according to physician recommendations. In the ASTEC trial, adjuvant therapy was balanced between the arms. In the Italian trial there was more adjuvant chemotherapy following lymphadenectomy and more radiation following no lymphadenectomy, presumably as a perceived need for systemic therapy in node-positive women.

Both trials, in which a totality of 2,000 women participated, showed very similar results. In both trials, there was no difference in either disease-free or overall survival. In the ASTEC trial, there was significantly better recurrence-free survival in the non-lymphadenectomy arm, but this effect disappeared when adjustment was made for preexisting tumor-related risk factors.

Some found the data convincing, others did not. The criticism of ASTEC in particular included insufficient lymphadenectomy in terms of node counts and lack of para-aortic dissection, but at least in ASTEC, adjuvant therapy did not confound the between-arm comparison, though some complained that the proportion who received radiation was high. It is widely accepted, however, that external beam radiation does not impact overall survival. There was also criticism of the high proportion of non-high-risk tumors, which they suggested would result in insufficient deaths such that the trial was underpowered, even though the trial fulfilled the a priori power calculation, in terms of survival rate and numbers recruited.

The idea that surgery could cure women with positive para-aortic nodes seems fanciful, though advocates of para-aortic dissection point to the potential for extended field radiation in node-positive women, and the fact that not all positive para-aortic nodes are associated with pelvic nodes. The skeptics who were unconvinced by the grade I evidence from randomized trials were pleased to see another retrospective study, this time from Japan, which showed an association between para-aortic dissection and improved survival. This so-called SEPAL study [25] compared outcomes from two centers, in one the standard practice was pelvic lymphadenectomy (PL) and in the other pelvic and para-aortic lymphadenectomy (PPL). Deaths from disease in the PL center were 60/194 (31 %), whereas it was only 33/213 (15 %) in the PPL center. The notable factors in this study were that adjuvant treatment was very different; 77 % had chemotherapy/1 % radiotherapy in the PPL center, and 45 % chemotherapy/39 % radiotherapy in the PL center, despite the overall node-positive rate being similar 24 % (PL) versus 29 % (PPL). The authors acknowledged the need for randomized trials which included para-aortic dissection.

So, why should women undergo a lymphadenectomy which randomized trials show does not confer benefit in terms of survival and which consumes resources? It is rational that accurately identifying node-negative women could spare them the toxicity and costs of adjuvant therapy, which is the main argument in favor of lymphadenectomy. Unpublished data from ASTEC show that though node-negative women have six times lower death rate than node-positive women, because of the far larger number of node negatives, the overall numbers of deaths in ASTEC was not grossly dissimilar:

Node positive 24/54, 44 % (95 % CI, 38–51 %)

Node negative 41/560, 7 % (95 % CI, 6.8–7.9 %)

These data suggest that there is a need to stratify adjuvant therapy based on overall risk rather than node status. In other words, node status by lymphadenectomy may not be a sensitive enough biomarker of death from disease, though it undoubtedly has a better positive predictive value than other risk factors considered individually. A comprehensive assessment of risk must include not only tumor-specific factors (grade, depth of myometrial invasion, lymphovascular space invasion) but also patient-specific factors (age, comorbidities, patient wishes), and lymph node status forms only part of that assessment. In the future, novel serum, tissue, or radiological biomarkers that correctly identify aggressive disease may facilitate individualized care for all.

But in the meantime, how can this gap between adjuvant therapy for all high risk and just for node-positive women be bridged? One possible strategy is sentinel node surgery. In an instructive French study published recently [36], sentinel node positivity by means of ultrasectioning and immunohistochemistry detected more women with positive nodes than conventional lymphadenectomy and necessitated less surgery with a reduced risk of lymphedema. The data from the study showed that among the 111 women with detectable sentinel nodes, nine (8 %) had nodal micrometastases detected by immunohistochemistry that had not been detected by conventional histopathology. While these could have been single positive nodes which had been prospectively removed as the sentinel node and, therefore, not available for detection by subsequent lymphadenectomy, they could represent the small proportion (7 % in ASTEC) of women with negative nodes who relapse. The French study demonstrated the feasibility and reliability of sentinel node biopsy, which lends itself to laparoscopic surgery, which is increasingly seen as preferable to open surgery for endometrial cancer.

The Impasse: Mayo and Manchester Meet

The "all-guns-blazing" strategy of the Mayo has been countered by the cold logic of the Manchester approach. Could we agree to "make love, not war"? The opposing views expressed in this paper probably require a major trial to compare the different management approaches which divide the pros and cons. Can we design a trial to reconcile our differences? It is unlikely that adding lymphadenectomy would alone achieve direct therapeutic efficacy; therefore, a trial designed to show a survival benefit based on lymphadenectomy alone would not be the optimal strategy. What is a valid arena for a trial is to address the issue of lymphadenectomy as a means of tailoring and selecting adjuvant therapy. The alternate hypotheses of such a trial could be (a) if all high-risk women were treated with adjuvant radiation and chemotherapy, survival would be better than if selected for adjuvant therapy based on nodal status and (b) selective adjuvant therapy could achieve equivalent survival with less toxicity and expense. The tumor characteristics and endpoints for such a trial would require:

1. A study population limited to high-risk endometrial cancer patients with a postsurgical recurrence risk of 15–20 %. (e.g., all G3 and non-endometrioid tumors based on preoperative or intraoperative pathology).
2. The need for quality control of the adequacy of lymph node dissection, in the "lymphadenectomy" arm. "Mayo" and "Manchester" have a different view of this issue. Manchester would accept a dissection to the level of the inferior mesenteric artery. While Mayo would require dissection up to the renal vessels. A possible solution to the disagreement would be to randomize stratifying by center, with every center stating the extent of para-aortic lymphadenectomy at the beginning of the trial.
3. Adjuvant treatment planning stratification to compare two philosophies: (a) the use of uterine factors alone or (b) the use of lymph node status to determine adjuvant management.
4. Overall survival and disease-related survival would be the primary endpoints.
5. Secondary endpoints would include recurrence-free survival, sites of recurrence, morbidity, quality of life, and healthcare costs.

The trial proposed poses a considerable challenge commanding an international effort. This could be achieved through the Gynecologic Cancer InterGroup (GCIG) with sufficient support. There will inevitably be great difficulty achieving broad consensus on trial design, such that the adjuvant therapy comparisons are sufficiently different. Figure 4.1 represents an example of a trial design that both sides may agree upon. It is a simple way of comparing a tailored adjuvant approach based on node status with an unselective approach based on the overall risk of grade 3 tumors. The trial should incorporate sentinel node detection and ultra-staging, at least in some centers.

Conclusion

The differing views on lymphadenectomy in endometrial cancer have not been reconciled based on the evidence base available, and without new trials, the uncertainty will continue. Sentinel node detection is the "new kid on the block" and offers a means of gaining information on nodal status without the effort of a full node dissection. This needs to be incorporated into future trials. Such trials need to be based on sufficiently high-risk disease, pelvic and para-aortic node dissection, and standardized adjuvant therapy regimens, which will comprise chemotherapy and stratification by radiation use to compare the two debated philosophies. This challenge should not go disregarded by the gynecologic oncology community.

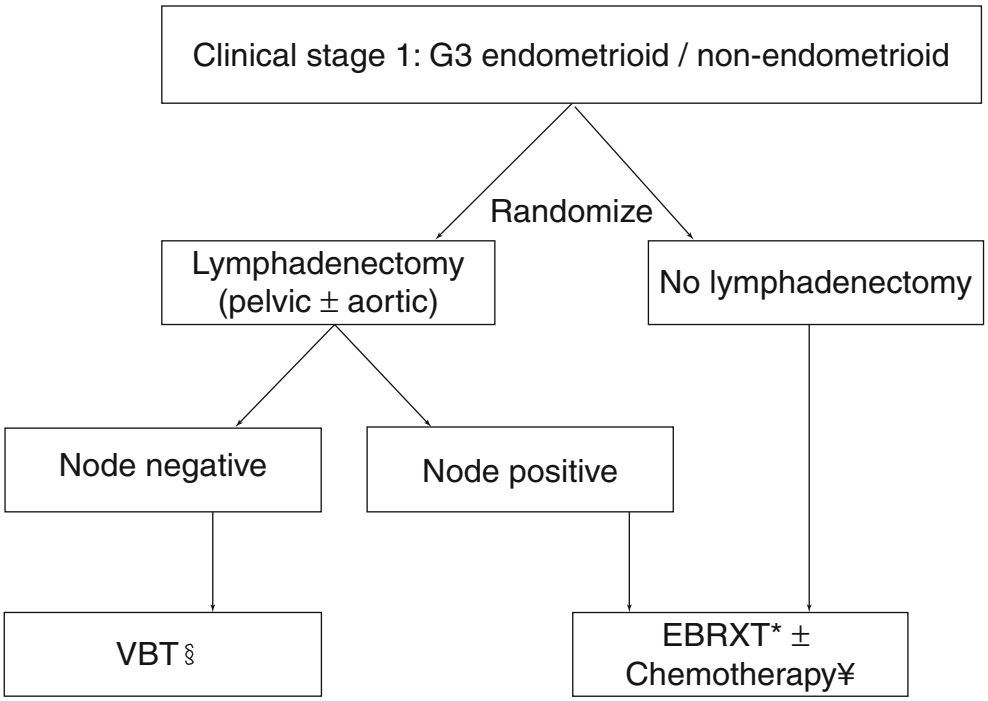

Fig. 4.1 High-risk endometrial cancer trial. *Aortic node positive receive extended field radiation, all receive pelvic radiation. (§) ENGOT-EN2-DGCG study. (¥) PORTEC 3/GOG 258. *VBT* vaginal brachytherapy, *EBRXT* external beam radiation, non-endometrioid (serous and clear cell)

Concluding Comments

- Resolution requires a trial to compare lymphadenectomy and selective adjuvant therapy with no lymphadenectomy and non-adjuvant therapy in high-risk endometrial cancer.
- Such a trial will require international collaboration.
- Future trials should incorporate sentinel node assessment.

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What Is the Role of Adjuvant Radiotherapy and Chemotherapy in Endometrial Cancer?

5

Thomas Hogberg and Carien L. Creutzberg

Summary Points

- Is adjuvant radiotherapy indicated for endometrial cancer (EC) patients?
- Is adjuvant chemotherapy indicated for EC patients? Based on which risk factors?
- If chemotherapy is used, should this replace radiotherapy or be used in combination?
- Should indications and types of adjuvant therapy be different for patients who had surgery with or without lymphadenectomy?

Introduction

Endometrial cancer (EC) is the most common gynecologic cancer in the western world. It is estimated that worldwide almost 300,000 women were diagnosed with EC and 75,000 died of the disease in 2008 [1]. EC mainly affects postmenopausal women with a median age between 65 and 70 years. Many patients have concurrent comorbidities, such as obesity, diabetes, and cardiovascular diseases. In the Northern European countries, the incidence rate (ESR, standardized to the European standard population) has remained unchanged over the past 10 years at approximately 17–18 per 100,000 women. The incidence in the United States is 23 per 10^5 women per year [2]. It is estimated that over the next two decades the absolute number of cases will increase by 32 % because of ageing and increasing obesity of the population [3]. EC generally has a good prognosis due to early diagnosis, with 75 % of patients having stage I disease, but per stage the survival is about the same as for ovarian cancer [4]. As reported in the FIGO (International Federation of Gynecology and Obstetrics) Annual Report [4], there is a substantial variation in survival rates among patients with stage I EC, with subgroups having a low or particularly high risk for micrometastatic disease (e.g., FIGO 2009 stage IA grade 1 and IB grade 3, respectively).

Bokhman proposed the concept of type I and type II endometrial carcinomas based on clinical behavior and histopathology [5]. Type I EC is estrogen-related tumors of the endometrioid type, developing from a background of endometrial hyperplasia, and have a good prognosis. Type II EC is non-estrogen-related, mainly poorly differentiated endometrioid, or non-endometrioid (e.g., serous and clear cell) carcinomas with a worse prognosis, arising from a background of atrophic endometrium. Modern molecular biology studies have further supported this classification [6, 7]. In the future, we may move away from the present classification system of tumors according to site of origin and histopathology towards a classification based on the molecular biologic traits driving the malignant behavior of individual tumors.

Risk Groups

The vast majority of patients are primarily treated with surgery (total hysterectomy and bilateral salpingo-oophorectomy). Major prognostic factors for endometrial carcinoma are stage, age, histological type, grade, depth of myometrial invasion, and presence of lymph-vascular space invasion (LVSI). Such clinical and histopathologic features predict micrometastatic disease. Pelvic (and para-aortic) lymphadenectomy (LA), if performed, informs about microscopic lymph node dissemination [8, 9].

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Adjuvant RT for endometrial carcinoma has increasingly been tailored to risk factors. Based on staging studies and prospective and retrospective data, endometrial carcinoma has been classified as low risk, intermediate risk, or high risk for lymph node metastases and/or early disease spread to the abdominal cavity and to distant sites. The majority of patients with EC have low- to intermediate- (55 %) or high-intermediate (30 %)-risk features; only 15 % have a high-risk profile. Five-year survival rates for patients with intermediate-risk EC are 80–85 %, with most of these patients dying of intercurrent diseases; rates of endometrial cancer death are 8–10 %.

Risk groups for stage I EC in the FIGO 2009 staging system [10]:

- *Low risk*: Stage IA grades 1–2 and endometrioid-type EC
- *Intermediate risk*: Stage IA grade 3 or IB grades 1–2 and endometrioid-type EC
- *High-intermediate risk*: Age of at least 60 years and/or LVSI and stage IA grade 3 or IB grades 1–2 and endometrioid-type EC
- *High risk*: IB grade 3 endometrioid-type EC or stages II–III or non-endometrioid types of EC

Controversial Issues Regarding Adjuvant Treatment for EC

1. Should adjuvant treatment be used for patients with high-intermediate-risk EC? Should indications and types of adjuvant therapy be different for patients who had surgery with or without lymphadenectomy?
2. What type(s) of adjuvant therapy should be given to patients with high-risk EC?

Is Adjuvant Radiotherapy Indicated for Patients with High-Intermediate Disease?

Pro

Four large randomized trials have investigated the role of external-beam pelvic radiation therapy (EBRT) in intermediate-risk EC, all showing that EBRT significantly reduced the risk of vaginal and pelvic relapse but without a survival difference (Table 5.1) [11–14]. After publication of these trials, the indication for EBRT was modified and became restricted to those EC patients with high-intermediate-risk features as defined in the PORTEC-1 and GOG#99 trials (Table 5.2). Important findings were that 75 % of the locoregional recurrences in the control arm were vaginal recurrences and that the salvage rate of vaginal relapse in previously unirradiated patients was high, with a 5-year overall survival of 70 % [17].

In order to investigate if vaginal brachytherapy (VBT) would be as effective as EBRT in preventing vaginal recurrence, the PORTEC-2 trial was initiated, in which 427 patients with high-intermediate-risk EC were randomly allocated to VBT (21 Gy high dose rate (HDR) in 3 fractions or 30 Gy low dose rate in 1 fraction to the proximal half of the vagina, specified at 5 mm from the surface of the cylinder) or EBRT (46 Gy, 23 fractions) (Table 5.1) [15]. The estimated 5-year vaginal recurrence rates were 1.8 % for VBT and 1.6 % for EBRT (HR 0.78, 95 % CI 0.17–3.49; $p=0.74$). The rates of isolated pelvic recurrences were 1.5 % versus 0.5 % (n.s.). The overall pelvic relapse rates were 5.1 % versus 2.1 % (n.s.); most of the pelvic relapses were also associated with distant metastases. There were no significant differences in 5-year OS and disease-free survival rates (85 % vs 80 % and 83 % vs 78 %, respectively) between the treatment arms. The rate of acute gastrointestinal grade 1–2

Table 5.1 Randomized trials of adjuvant radiation therapy in stage I endometrial carcinoma

Trial (ref) accrual period	No. pts eligibility	Surgery	Randomization	Locoregional recurrence	Overall survival
Aalders et al. [11] 1968–1974	540 St I	TAH-BSO	VBT vs VBT + pelvic RT	7 % vs 2 % at 5 years $P<0.01$	89 % vs 91 % at 5 years NS
Creutzberg et al. PORTEC-1 [12] 1990–1997	714 St IB gr 2–3 St IC gr 1–2	TAH-BSO	NAT vs pelvic RT	14 % vs 4 % at 5 years $P<0.001$	85 % vs 81 % at 5 years $P=0.31$ NS
Keys et al. GOG-99 [13] 1987–1995	392 St IB, IC, St II (occult)	TAH-BSO and lymphadenectomy	NAT vs pelvic RT	12 % vs 3 % at 2 years $P<0.01$	86 % vs 92 % at 4 years $P=0.56$ NS
Blake et al. ASTEC/EN5 [14] 1996–2005	905 St IA–B gr 3, St IC, St II, serous/cc	TAH-BSO ± lymphadenectomy	NAT vs pelvic RT	7%[a] vs 4 % at 5 years $P=0.038$	84 % vs 84 % at 5 years $P=0.98$ NS
Nout et al. PORTEC-2 [15] 2002–2006	427, age >60 St IB gr 3 or IC gr 1–2	TAH-BSO	VBT vs pelvic RT	2 % vs 2 % at 5 years $P=0.74$ NS	85 % vs 80 % at 5 years $P=0.57$ NS

Gr grade, *NAT* no additional treatment, *NS* not significant, *RT* radiation therapy, *St* stage, *TAH-BSO* total abdominal hysterectomy and bilateral salpingo-oophorectomy, *VBT* vaginal brachytherapy

[a]53 % in NAT arm received VBT; *isolated* locoregional recurrence reported

Table 5.2 Comparison of the high-intermediate-risk groups in the PORTEC and GOG-99 trials

	High-intermediate-risk groups	
Risk factors	PORTEC [12]	GOG-99 [13]
Age	<60 vs >60	<50 vs <70 vs >70
Grade	Grades 1–2 vs 3	Grade 1 vs 2–3
Deep invasion	<50 % vs >50 %	<66 % vs >66 %
Lymphovascular space invasion	–	Absent vs present
High-intermediate-risk (HIR) group	At least 2 of the 3 factors	Any age and 3 factors Age ≥50 and 2 factors Age ≥70 and 1 factor
Results for the HIR group	10-year locoregional relapse [16] RT: 5 % NAT: 23 % Rel. risk: 0.22	4-year relapse (any) RT: 13 % NAT: 27 % Rel. risk: 0.48

GOG Gynecologic Oncology Group, *PORTEC* Postoperative Radiation Therapy in Endometrial Carcinoma, *NAT* no additional treatment, *RT* radiation therapy

toxicity at completion of radiotherapy was 13 % in patients who had vaginal brachytherapy, which was significantly lower than in the EBRT group (54 %). The quality of life data was reported separately and was evaluated with the EORTC QLQ C30-core questionnaire and subscales for bladder, bowel, and sexual symptoms from the prostate cancer (PR25) and ovarian cancer (OV28) modules [18]. Eighty-one percent of the patients were evaluable for quality of life. Patient functioning was at the lowest level at baseline after surgery and increased during and after radiotherapy to reach a plateau after 12 months. Patients in the VBT group reported significantly better social functioning and lower symptom scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities because of bowel symptoms than patients in the EBRT group. At baseline, 15 % of patients were sexually active; this increased significantly to 39 % during the first year with no difference between the treatment groups. The quality of life scores of patients who had VBT were not different from that of an age- and sex-matched normal population [19]. In view of the similar vaginal control rates, vaginal brachytherapy should be preferred from a quality of life perspective when choosing adjuvant radiotherapy for patients with high-intermediate-risk EC.

As adjuvant radiotherapy (either EBRT or VBT) has no impact on overall survival and is primarily used to maximize local control, it has been debated that patients with (high) intermediate-risk EC should be observed after surgery, using radiation therapy only for salvage treatment in case of vaginal relapse. Obviously, the use of adjuvant EBRT should be limited to patients at sufficiently high risk of locoregional relapse to warrant the risk of treatment-associated morbidity. However, the 10-year locoregional relapse rates in the PORTEC-HIR (high-intermediate-risk) group were 4.6 % in the RT group and 23.1 % in the control group [16]. In the GOG-99 trial, EBRT provided a reduction of isolated 4-year local relapse in the HIR group from 13 to 5 % [13]. As the PORTEC-2 trial has shown VBT to be equally effective as EBRT in maximizing vaginal control, there is thus an adjuvant treatment modality available which causes only minimal short-term side effects and has no adverse impact on quality of life. Observing patients with HIR EC after surgery would mean leaving them at about 20 % (1 in 5) risk of locoregional relapse, 75 % of which are vaginal relapses which could have been easily prevented. Salvage treatment at the time of vaginal relapse with EBRT and VBT causes significantly more side effects and a 3–5 % risk of grade 3 late gastrointestinal complications. The stress and anxieties of watchful waiting and being diagnosed with a cancer recurrence are substantial and have a significant psychological impact. Given the trade-off between watchful waiting at a 1 in 5 risk of recurrence and having a simple and effective preventive treatment with the same long-term quality of life outlook, most patients likely would prefer the latter option. As long as no randomized trial is available which has fully investigated the impact and outcome of the watchful waiting option, VBT should continue to be the standard adjuvant treatment for EC patients with high-intermediate-risk features.

Con

Given the solidly proven fact that adjuvant radiotherapy has no impact on survival of patients with HIR EC [14, 20], it is clear that adjuvant vaginal vault irradiation is not cost-effective. Using data from the first PORTEC trial [12], it could be expected that observing 100 high-intermediate-risk patients for 5 years after no adjuvant therapy has been given, one would expect 14 vaginal recurrences. About 70 % of those can be salvaged with radiotherapy at the time of relapse. According to the PORTEC-2 trial, two vaginal recurrences would be expected after vaginal brachytherapy. It seems that treating 100 women with VBT would save 12 from vaginal recurrence, and ultimately the outcome would be the same (2 uncontrolled recurrences). The number of women needed to treat to avoid 1 vaginal recurrence is

estimated to be 8 [21]. Even if the side effects from VBT are minor [19], 100 patients will be at risk for such side effects, while only 12 will benefit. Standard adjuvant brachytherapy for all patients would mean inefficient use of health-care facilities and health-care budgets. Patients should be followed closely after surgery, especially in the first 2–3 years, and monitored for local relapse.

Should Adjuvant Therapy Be Different if Surgery Included Lymphadenectomy or Not?

Pro

Lymphadenectomy (LA) was introduced in the FIGO 1988 staging system. Staging is mainly a procedure to assure comparability when reporting statistics on clinical results. Stage is also one of several important factors in the decision-making process. More thorough staging with LA could potentially identify patients with nodal metastases curable with adjuvant therapy [22]. It might also be beneficial by removing occult small-volume metastatic disease that remains undetected by the pathologist. Another potential benefit of LA could be that adjuvant radiotherapy could be avoided in lymph node-negative patients. The performance of LA is mostly supported by retrospective studies [23–25]. The Japanese SEPAL study is another retrospective study, which compared two hospitals with policies mainly differing as regards LA [26]. Hokkaido Cancer Center performed pelvic LA ($n=325$), and Hokkaido University Hospital performed pelvic and para-aortic LA ($n=346$). The survival was significantly better in the patient cohort treated at the hospital using pelvic and para-aortic LA, both in the intermediate- and high-risk groups. The postoperative treatment was, however, also different. In the group with only pelvic LA, 23 % received radiotherapy and 27 % chemotherapy, while 47 % in the group with pelvic and para-aortic LA were treated with adjuvant chemotherapy and only 1 % with radiotherapy. A multivariate analysis showed better survival associated with para-aortic LA and chemotherapy. LA therefore has a significant impact on the indications for adjuvant therapy.

If a patient has node-negative stage I–II EC confirmed by LA, this is even more reason to refrain from adjuvant treatment, as retrospective studies have suggested the risk of relapse to be lower than in patients of similar stage who had no LA.

Con

Two randomized trials have been published, neither showing any differences in OS or progression-free survival (PFS) between the arms with and without LA for patients with stage I EC [27, 28]. A Cochrane report has analyzed the pooled results [29]. There was a nonsignificant trend to a slightly better PFS and OS in the non-LA group. The direct surgical morbidity was not different, while risk for the surgically related systemic morbidity was 3.7 times higher in the LA group (95 % CI 1.04–13.3), and the risk for the development of lymphocysts or lymphedema was 8.4 times higher (95 % CI 4.1–17.3) in the LA group. In the ASTEC trial, there was a second randomization to radiotherapy or observation not depending on nodal status [14, 27]. Women who had LA had more radiation-related complications [14]. In the GOG-99 trial where all patients had LA and were lymph node negative, the subgroup with HIR features had still a significant reduction of the risk of relapse with EBRT and worse survival in the observation arm [13]. Risk factors such as grade 3 and LVSI are highly significantly associated with risk of relapse, both locally and at distant sites, and are both associated with the risk of microscopic nodal and distant metastases and with relapse in LA-confirmed node-negative patients. LA can detect microscopic nodal spread but cannot alter the course of disease as this is associated with distant metastases, as shown by the overlapping survival rates. LA does not obviate the need for adjuvant therapy in the presence of high-risk factors and thus primarily adds to toxicity.

Which Adjuvant Treatment Modality(ies) Should Be Given to Patients with High-Risk Tumors?

Radiotherapy

Pro

The randomized studies on radiotherapy versus observation have accrued few patients with high-risk tumors. In the meta-analysis of the ASTEC/EN5 report of PORTEC-1, GOG-99, and ASTEC/EN5 trials, the total number of high-risk patients was 334 [14]. The hazard ratio in the high-risk group was 0.88 (95 % CI 0.59–1.29) for OS and 0.81 (0.50–1.30) for disease-specific survival favoring radiotherapy. The Cochrane meta-analysis [20] came to the same conclusion that there was a trend towards a survival benefit for patients with multiple risk factors, including FIGO 2009 stage IB grade 3, and that radiotherapy may be justified. There were 227 patients in their analysis of patients with high-risk tumors. The HR for endometrial carcinoma-related deaths was 0.65 (95 % CI 0.38–1.14) and for OS 0.76 (95 % CI 0.49–1.19). Two randomized trials of pelvic EBRT alone compared to adjuvant chemotherapy alone (3 or 5 cycles of cyclophosphamide, doxorubicin, and cisplatin, CAP) have shown identical overall and relapse-free survival (RFS) rates in both arms [30, 31]. Patients who received adjuvant chemotherapy had a delay of distant relapse, and those treated with EBRT had a delay of pelvic relapse, but in the end, RFS and OS were the same. As EBRT has fewer side effects than adjuvant chemotherapy, these results indirectly support the

Table 5.3 Phase II and III chemotherapy studies in advanced or recurrent endometrial cancer

Reference	Type of trial	Intervention	*n*	Study population	ORR (%)	mPFS months	mOS months
Aapro et al. [36]	Phase III	Doxorubicin	87	Chemonaïve	17	7	7
		Doxorubicin + cisplatin	90		43	8	9
Thigpen et al. [37]	Phase III	Doxorubicin	150	Chemonaïve	25	4	9
		Doxorubicin + cisplatin	131		42	6	9
Fleming et al. [38]	Phase III	Doxorubicin + cisplatin	129	Chemonaïve	34	5	12
		Doxorubicin + cisplatin + paclitaxel	134		57	8	15
Hoskins et al. [39]	Phase II	Paclitaxel-carboplatin	63	Mixed	61	n.r.	n.r.
Sorbe et al. [40]	Phase II	Paclitaxel-carboplatin	66	Mixed	67	14	26
Akram et al. [41]	Retrospective phase II	Paclitaxel-carboplatin	18	Chemonaïve	63	24	27
Michener et al. [42]	Retrospective phase II	Paclitaxel-carboplatin	22	Mixed	87	n.r	n.r.
Scudder et al. [43]	Phase II	Paclitaxel-carboplatin	47	Chemonaïve	40	7	14
Arimoto et al. [44]	Phase II	Paclitaxel-carboplatin	37	Mixed population	61	n.r	n.r.
Sovak et al. [45]	Retrospective phase II	Paclitaxel-carboplatin	85	Mixed	43	5	13
Homesley et al. [46]	Phase II	Liposomal doxorubicin	52	Chemonaïve	12	n.r.	11
Du Bois et al. [47]	Phase II	Liposomal doxorubicin + carboplatin	27	Mixed population	44	10	21
Pignata et al. [48]	Phase II	Liposomal doxorubicin + carboplatin	42	Chemonaïve	60	12	18
Vandenput et al. [49]	Phase II	Paclitaxel + carboplatin	30	Chemonaïve	74	13	23

mPFS median progression-free survival, *mOS* median overall survival, *n* number of patients, *n.r.* not reported, *ORR* overall response rate

use of adjuvant EBRT. A retrospective analysis of 71 patients with stage IIIC EC (43 pelvic node positive, 28 para-aortic node positive) showed that OS (73 vs 40 %), disease-specific survival (78 vs 39 %), and survival without pelvic relapse (98 vs 61 %) were significantly higher in patients who had EBRT as adjuvant treatment (50 had EBRT alone, 16 EBRT with weekly cisplatin), compared to 18 patients who had chemotherapy alone [32]. Mundt et al. [33] similarly reported a substantial (40 %) rate of pelvic failures in a retrospective analysis of 43 patients with high-risk or advanced-stage EC who received adjuvant chemotherapy alone: 67 % relapsed, of whom 40 % had pelvic recurrence and 56 % distant relapse. The 3-year pelvic failure rate was 47 %, and in 31 % the pelvis was the first or only site of recurrence. EBRT remains the most effective adjuvant treatment ensuring pelvic control, with a modest overall survival improvement.

Con

There are no randomized studies unequivocally supporting the use of radiotherapy in this risk group. The randomized trials of EBRT versus CAP chemotherapy have failed to show any difference between chemotherapy and EBRT for both RFS and OS [30, 31].

Chemotherapy

Pro

Phase 2 studies on chemotherapy in advanced or metastatic endometrial cancer have shown response rates exceeding 20 % mainly with anthracyclines, platinum compounds, and taxanes [34, 35] (Table 5.3). Two randomized studies compared doxorubicin + cisplatin (AP) with doxorubicin (A) [36, 37]. Both studies found that the combination gave better response rates but no significant differences in survival. AP was for many years regarded as the standard in endometrial cancer. The Gynecology Oncology Group (GOG) tested the addition of paclitaxel (T) to AP in 273 (263 eligible) women with advanced or metastatic endometrial cancer of any cell type [38]. Response rate (57 % vs 34 %), PFS (median 8.3 vs 5.3 months), and OS (median 15.3 vs 12.3 months) were significantly better with TAP. However, the TAP combination was toxic—the rate of grade 2–3 peripheral neurotoxicity was 39 % compared with 5 % in the AP arm. All women in the TAP arm received a granulocyte stimulator. The imbalance in the number of possibly treatment-related deaths (five on TAP vs none on AP) is of note. However, only two of the five deaths (neutropenic fever and AML) were, according to the authors, clearly treatment related. The modest gains and the reservations about the toxicity of this regimen may have precluded widespread use.

Paclitaxel and carboplatin (TcP) is a commonly used well-tolerated drug combination in gynecologic cancer. However, neurotoxicity is still problematic. Phase 2 studies and retrospective studies in endometrial cancer have demonstrated high response rates (40–90 %) [39–41, 43–45]. The Japanese Gynecologic Oncology Group (JGOG) compared the efficacy and safety of the different combinations of taxanes and platinum agents, i.e., TcP, docetaxel + cisplatin (DP), docetaxel + carboplatin (DcP), and paclitaxel + cisplatin (TP) in JGOG-2041, a phase II randomized study [50]. TP was eliminated, as the results of clinical trials for ovarian cancer had revealed a strong neurotoxicity compared with

TcP. The response rates of the three regimens were not inferior to AP therapy, and the toxicity was acceptable. The response rate to DcT (48 %) was somewhat lower, although not significantly, than to TcP (60 %) and DP (52 %), and TcP and DP were therefore selected for comparison with AP in a randomized phase III trial, JGOG-2043, in advanced cases with residual tumors no greater than 2 cm, and patients with stages I and II with invasion to more than half of the myometrium and histological grade 2 or 3 of all cell types [51]. JGOG-2043 has closed, but the final results have not yet been reported.

Despite the lack of evidence from randomized trials, many centers have used paclitaxel and carboplatin as a standard adjuvant regimen in endometrial cancer in daily practice. Recently, preliminary results of GOG-209 comparing TcP with TAP were presented at the Society of Gynecologic Oncology's Annual Meeting on Women's Cancer 2012 [52]. The trial recruited 1,381 patients (1,312 evaluable), and the results of a planned second interim analysis based on 551 deaths were presented. The two chemotherapy regimens were of similar efficacy. With a median follow-up exceeding 4 years, the median PFS was 14 months in both trial arms, and the median OS was 32 months for TcP versus 38 months for TAP (HR 1.01). A higher percentage of patients on TcP were able to complete all seven planned courses of treatment (69 % vs 62 %). The toxicity rates favored TcP, which was less toxic except for neutropenia (79 % vs 52 %). However, the incidence of neutropenic fever was similar for both regimens (6 % vs 7 %). These preliminary results have shown that TcP was not inferior to and was less toxic than TAP.

GOG-122 was a pivotal study that changed opinion about chemotherapy of EC in many people [53]. Patients with FIGO 1988 stage III or IV EC of any histology were randomized after surgical staging and optimal tumor resection (no single site of residual tumor greater than 2 cm) to chemotherapy (AP every 3 weeks for 7 cycles, followed by one cycle of cisplatin) or whole abdominal irradiation (WAI) (30 Gy in 20 fractions, with an additional 15 Gy pelvic boost). The trial recruited 422 (396 evaluable) patients, of whom 194 were allocated to chemotherapy and 202 to WAI. Both PFS and OS were significantly better for patients in the chemotherapy arm. The results were presented and analyzed for significance adjusted for stage, which is unusual for randomized studies and has been criticized. The unadjusted Kaplan-Meier estimates for 5-year PFS were 42 % versus 38 % and for OS 53 % versus 42 % in the chemotherapy and WAI arm, respectively. This should be compared with the adjusted values of 50 % versus 38 % and 55 % versus 42 %. The authors did not present P values for the unadjusted results. The treatment effect was consistent in subgroup analyses according to stage, substage, age, and residual disease status. The recurrence rate between the two arms differed by only 4 % (50 % vs 54 %). A possible explanation for the difference in OS despite small differences in PFS and recurrence rate is that second-line treatments might have a greater efficacy in those patients that had no previous irradiation. Grade 3 and 4 adverse effects (particularly hematologic, gastrointestinal, cardiac, and neurologic) were significantly more common in the chemotherapy arm. Treatment may have contributed to the death of five patients in the WAI arm and eight patients assigned to chemotherapy. The use of WAI in this setting has been debated as the dose and volume were not suitable in this patient population, but chemotherapy has been shown to improve survival in this group of fairly advanced EC.

Con

Both the Italian and Japanese trials cited above compared adjuvant CAP chemotherapy versus adjuvant pelvic EBRT [30, 31]. The Italian study randomized 345 (340 evaluable) patients with endometrioid or adenosquamous carcinoma and FIGO 1988 stage IC grade 3 or stage IIA to IIB grade 3 with ≥50 % myometrial invasion or FIGO stage III (67 % of patients had stage III EC) [31]. The Japanese trial randomized 475 women with stage IC to IIIC with 50 % MI or greater; in this trial, most patients had early disease stage, and many had at most intermediate-risk factors [30]. Both studies failed to show any superiority of chemotherapy. The much-cited GOG#122 trial was not a true adjuvant trial as it included patients with residual disease. WAI in the radiotherapy arm was a modality and dose regimen unsuitable for patients with this advanced disease stage. Also toxicity comparisons were made between WAI and a very intensive chemotherapy regimen of APx8, which would not be used in current practice [53]. While the unadjusted analyses showed modest survival improvement favoring chemotherapy, event rates were very similar (50 vs 54 %), and chemotherapy seemed to delay rather than cure microscopic metastases. There is as yet no single randomized trial of chemotherapy used in the adjuvant setting for stage I–III disease which has shown superiority of chemotherapy alone for either relapse-free or overall survival while imposing significant adverse effects such as short-term complete hair loss, nausea and vomiting, and long-term neurological symptoms to elderly patient groups with frequent comorbidities. While long-term quality of life effects from EBRT have been extensively studied, none of the adjuvant chemotherapy trials have included long-term quality of life after chemotherapy.

Chemotherapy and Radiotherapy Combined

Pro

The Nordic Society of Gynecologic Oncology (NSGO) in collaboration with the European Organization for the Treatment and Research on Cancer (EORTC) compared sequential adjuvant radiotherapy and chemotherapy with radiotherapy in 383 patients (378 evaluable) [54]. Various chemotherapy combinations were used, mainly doxorubicin-cisplatin or epirubicin-cisplatin (83 %), but also

Table 5.4 Randomized trials investigating adjuvant chemotherapy and/or radiotherapy in endometrial cancer

Trial (ref)	No. patient eligibility/stage	Randomization	Pelvic recurrence	OS PFS
Susumu et al. [30]	385 St I–III with >50 % MI (60 % St IB)	Pelvic RT vs CT CAPx3	7 % vs 7 % NS	85 % vs 87 % NS 84 % vs 82 % NS
Maggi et al. [31]	345 St IB–II gr 3 (35 %) St III (65 %)	Pelvic RT vs CT CAPx5	12 % vs 16 % NS	69 % vs 66 % NS 63 % vs 63 % NS
Randall et al. [53]	396 St III; IV (28 %) (residual <2 cm)	WAI vs CT APx7 + Px1	13 % vs 18 %	42 % vs 53 % $P<0.01$
Morrow et al. [55]	181 clinical St I–II 31 % node+	Pelvic RT vs pelvic RT and CT (Ax6–8)	N/A	No difference
Kuoppala et al. [56]	156 Stage IA g3, St IB, St II–IIIA (46 % stage IB)	Pelvic RT vs pelvic RT and CT (CEPx3)	3 % vs 2 % NS	85 % vs 82 % DSS NS N/A
Hogberg et al. [54] (pooled data NSGO/EORTC with ILIADE-III)	NSGO/EORTC: 382 St I–III; St I serous (49 % St IB). ILIADE: 157 St II–III	Pelvic RT vs pelvic RT and CT (4 cycles)	N/A	75 % vs 82 % NS 69 % vs 78 % $P=0.009$

A doxorubicin, *AP* doxorubicin + cisplatin, *CAP* cyclophosphamide + doxorubicin + cisplatin, *CEP* cyclophosphamide + epirubicin + cisplatin, *CT* chemotherapy, *DSS* disease-specific survival, *N/A* not available, *NS* not statistically significant, *P* cisplatin, *RT* radiation therapy, *St* stage, *VBT* vaginal brachytherapy, *WAI* whole abdominal radiotherapy

paclitaxel-carboplatin (10 %), epirubicin-carboplatin (4 %), and paclitaxel-epirubicin-carboplatin (3 %) given after RT (69 %) or before RT (17 %, 4 % unknown). This trial was the first to show a significant 7 % increase in 5-year PFS with the addition of chemotherapy to RT from 72 to 79 %, HR 0.64 (95 % CI 0.41–0.99; $P=0.04$), but no significant difference in overall survival. The EORTC/NSGO trial was published together with the ILIADE-III study from the MaNGO group (see Table 5.4). In the pooled data analysis with ILIADE-III (157 patients, for a combined total of 534 evaluable patients), results were similar, with a statistically significant difference in 5-year PFS favoring the combined arm: 78 % for combined RT + CT versus 69 % for RT alone, HR 0.63 (95 % CI 0.44–0.89; $P=0.009$), but only a trend for improved 5-year OS (82 % vs 75 %, HR 0.63; 95 % CI 0.46–1.03; $P=0.07$). For cancer-specific survival, the difference was significant (87 % vs 78 %, HR 0.55; 95 % CI 0.35–0.88; $P=0.01$). In the NSGO/EORTC trial, there was one treatment-related death 3 months after randomization in the radiation arm. No further details were available. There were eight serious adverse events (SAE) in the CT + RT arm and one in the RT arm. All SAEs resolved after appropriate treatment. In the MaNGO trial, no treatment-related death was registered. It should be noted that although NSGO/EORTC and GOG-122 trials both showed a PFS benefit with chemotherapy for the overall trial populations, neither showed a trend for PFS or OS benefit from adjuvant chemotherapy for the subpopulations of patients with serous or clear cell tumors, although these were few in number ($n=140$ in NSGO/EORTC and $n=100$ in GOG-122). The hazard ratios for PFS and OS with chemotherapy were 0.91 and 1.02 for patients with serous or clear cell cancer in GOG-122 and 0.83 and 0.94, respectively, in the NSGO/EORTC trial. However, the GOG has analyzed their trials of chemotherapy in patients with advanced or metastatic endometrial cancer [57]. They found no evidence that serous or clear cell carcinomas responded differently to chemotherapy than endometrioid carcinomas. The problem is that these tumors comprise rather small subgroups in the trials leading to inconclusive results. Thus, there is a need to establish the efficacy of adjuvant chemotherapy for serous and clear cell cancers in separate randomized trials.

The Radiation Therapy Oncology Group (RTOG) has published a phase II study (RTOG-9708) of combined adjuvant pelvic radiation (45 Gy + vaginal brachytherapy) with concomitant cisplatin on days 1 and 28, followed by four courses of TP at 4-week intervals [58]. Patients with grade 2 or 3 endometrial adenocarcinoma with either >50 % MI, cervical stromal invasion, or pelvic-confined extrauterine disease were eligible. This treatment was feasible with excellent locoregional control suggesting additive effects of chemotherapy and radiation. Distant metastases continued to occur in more advanced-stage patients.

Con

Two small studies of RT versus combined RT + CT have been published. In a historical GOG study (GOG-34, published in 1990), sequential adjuvant radiotherapy followed by single agent doxorubicin chemotherapy was compared with adjuvant EBRT alone in 224 patients (only 181 evaluable) [55]. Eligible patients had FIGO 1988 stage I and II (occult) EC, with one or more of the following high-risk features: ≥50 % myometrial invasion, pelvic or para-aortic metastases, cervical extension (occult), or adnexal metastases. After EBRT, patients were randomized to observation or to doxorubicin 45 mg/m^2. The study was terminated prematurely because of slow recruitment and was flawed as 27 % of women randomized to doxorubicin did not receive it, and many patients were lost to follow-up. No significant differences in OS or PFS were found. The authors concluded that the study was inconclusive due to small sample size and protocol violations.

A randomized Finnish study compared split-course pelvic EBRT (2×28 Gy separated by a pause of 3 weeks) with

EBRT combined with one course of chemotherapy (cyclophosphamide 500 mg/m^2 + E 60 mg/m^2 + P 50 mg/m^2; CEP) given before EBRT, one in the radiation pause, and one after EBRT [56]. Eligible patients had FIGO 1988 stage IA–B grade 3 or IC–IIIA grade 1–3. No significant survival difference could be found (age-adjusted HR 1.21; 95 % CI 0.56–2.65), while more toxicity was reported in the combination arm, most notably severe bowel toxicity 9.5 % versus 2.8 %. This trial again is inconclusive because of the small sample size rendering it underpowered and the use of a historical split-course EBRT schedule. With two small trials being inconclusive and the larger NSGO/EORTC trial showing only a modest 7 % PFS difference (9 % in the pooled analysis) without a statistically significant OS difference, the advantages of combining RT and CT have not been proven. Combining EBRT and CT leads to more acute toxicity, and long-term results are lacking.

Ongoing and Planned Trials

Ongoing trials investigating the roles of adjuvant chemotherapy, radiation therapy, and combinations of CT + RT are the PORTEC-3, GOG#249, and GOG#258 trials (see Table 5.5). The international randomized PORTEC-3 trial [59] has been based on the RTOG phase II study [58]. Patients with high-risk EC (FIGO 2009 stage IA grade 3 LVSI+; stage IB grade 3; stage II; stage IIIA or IIIC; stage IIIB [if parametrial invasion]; or serous or clear cell histology of stage IA [with myometrial invasion], stage IB, stage II or III disease after surgery with no residual macroscopic tumor are eligible). PORTEC has substituted paclitaxel and cisplatin used in the RTOG pilot with paclitaxel and carboplatin (TcP; 2 cycles of cisplatin concurrent with RT and 4 cycles of TcP after RT) [64]. The primary end points are OS and failure-free survival at 5 years. Secondary end points are quality of life, severe treatment-related morbidity, rate of vaginal or pelvic relapse, and rate of distant metastases. The trial uses a uniform treatment schedule starting both treatment modalities early and includes upfront pathology review to ensure that only patients with true high-risk tumors are included and quality of life assessments to establish short- and long-term toxicities and their impact on the patient's daily life. With international intergroup collaboration, patient accrual is well underway (570 of the planned 670 patients recruited).

GOG-249 is a randomized trial comparing EBRT alone with VBT and 3 cycles of TcP; primary end point is RFS [60]. Eligible patients have stage I or II EC with high-intermediate- or high-risk factors; recruitment is fast, and the target of 562 patients may be reached in 2013. GOG-258, the companion trial for advanced-stage EC, is comparing 6 cycles of TcP chemotherapy alone with the same combined CT + RT schedule as in PORTEC-3. Eligible patients have stage III–IVA EC, optimally debulked [61]. Finally, the ENGOT-EN2-DGCG trial has recently started [62]. Patients with node-negative (LA required) stage I grade 3 or stage II endometrioid adenocarcinoma or stage I–II clear cell, serous, or squamous carcinoma will be randomized to six courses of TcP versus observation. VBT is optional in both arms. The PORTEC-4 trial has also recently started; this trial is randomly comparing adjuvant vaginal brachytherapy and observation (2:1 randomization) and two dose levels of VBT (1:1) in patients with high-intermediate-risk EC [63].

These trials will be able to answer many of the present questions and controversies regarding optimal use and optimal schedules of adjuvant therapy for women with high-risk and high-intermediate-risk EC.

Other trials addressing the role of lymphadenectomy in high-risk EC and of targeted drugs are needed to resolve ongoing controversies. Unfortunately, the emergence of predictive tests for targeted drugs often lags behind the introduction of new drugs. The signal pathways that at present have been targeted in clinical trials in endometrial cancer are the inhibition of EGFR, VEGFR, and PI3K/PTEN/AKT/mTOR signal pathways, of which multitarget VEGF inhibitors are presently considered most promising [7, 65].

Table 5.5 Ongoing and planned trials investigating adjuvant chemotherapy and/or radiotherapy in endometrial cancer

Trial (ref)	Planned no. eligibility/stage	Randomization	Accrual period
PORTEC-3 [59]	670 St I–III with high-risk factors; serous/cc	Pelvic RT vs RT-CT (Px2 during RT and TcPx4)	To be completed in 2013
GOG-249 [60]	562 St I–II with high-risk factors or serous/cc	Pelvic RT vs VBT and CT (TcPx3)	To be completed in 2013
GOG-258 [61]	804 St III/IV all cell types	RT-CT (Px2 during RT and TcPx4) vs CT (TcPx6)	To be completed in 2015
ENGOT-EN2-DGCG [62]	678 St I grade 3 or St II or St I–II non-endometrioid	CT (TcPx6) vs observation (both arms ± VBT)	Started 2012
PORTEC-4 [63]	500 St IA grade 3 and age >60; St IB grades 1–2 and age >60 or LVSI+	VBT (2 dose levels) vs observation	Started 2012

CT chemotherapy, *P* cisplatin, *RT* radiation therapy, *St* stage, *TcP* paclitaxel + carboplatin, *VBT* vaginal brachytherapy

Concluding Comments

- Patients with low- and intermediate-risk tumors should be observed after surgery.
- Patients with high-intermediate-risk tumors should either have postoperative vaginal brachytherapy or be followed closely and treated promptly at the time of relapse.
- Patients with high-risk tumors need adjuvant therapy and should be included in randomized studies to determine the optimal approach, both with regard to efficacy and quality of life.

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Chemotherapy and/or Targeted Therapies for Advanced Endometrial Cancer: Time to Rethink?

6

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Summary Points

- Historically, chemotherapy forms the backbone of standard treatment for endometrial cancer. Can the published data forming the basis of this recommendation be easily applied to the world of oncology today, or is there a need for updated information in the era of increased molecular profiling of tumors?
- Given the demographics of patients with endometrial cancer, can we aim for a more individualized approach to treatment which takes into account relevant prognostic molecular information, patient health, and quality of life preferences?
- Are the data available regarding novel targeted agents sufficient to propose a new standard for therapy?

Introduction

Ninety-five percent of cancers of the uterine corpus are carcinomas [1]. Most endometrial carcinomas present at an early stage and are cured by surgery with or without radiotherapy. As a result, advanced or recurrent endometrial carcinoma has been perceived as a rare tumor. However, the American Cancer Society estimates that about 8,100 women in the United States will die from cancers of the uterine body in 2011 and advanced or recurrent endometrial cancer remains an incurable disease with limited treatment options. Data from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) program suggest that the 5-year relative survival for women with metastatic uterine cancer between the years 2001 and 2007 was only 15.9 % and the median survival only 12 months.

Should Chemotherapy Be the Standard Treatment?

Considerable data exist regarding the utility of chemotherapy in the context of recurrent and metastatic endometrial cancer, the majority of which precede the era of targeted therapy options. As such, conventional chemotherapeutic agents represent the mainstay of treatment for endometrial cancer and constitute the standard of care to which all new treatments should be compared.

A number of chemotherapy agents are active in the treatment of endometrial cancer. Platinum drugs, anthracyclines, and taxanes have produced 20–30 % single-agent response rates in women with chemotherapy-naïve advanced endometrial cancer [2] (Table 6.1). Given the known activity of free doxorubicin, pegylated liposomal doxorubicin produced a disappointingly low response rate of 11.5 %. Interestingly, it produced almost the same level of activity in women with pretreated disease (9.5 %), raising the question of whether some unknown adverse selection factors were present in the women treated on the frontline trial (e.g., since up-front combination chemotherapy was already established at the time, perhaps less fit patients elected to participate in a trial of single-agent liposomal doxorubicin). 5-Fluorouracil has been reported to produce response rates in the range of 20 %, but the trials testing this agent are older and somewhat difficult to interpret with modern benchmarks. Alkylating agents

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and vinca alkaloids generally have shown lower levels of activity and significant toxicities at the doses and schedules tested [3].

Is Combination Drug Therapy Superior to Single-Agent Chemotherapy?

Combination chemotherapy produces higher response rates than single-agent therapy. It should be realized, however, that this does not always translate into improved survival and the risk factors common in the endometrial cancer population such as advanced age (median age at diagnosis around 65 years), poor performance status, medical comorbidities, and a history of prior pelvic radiation may increase the risk of chemotherapy associated toxicities [4]. Nonetheless, with dose reductions and/or growth factor support, treatment is usually tolerable, and combination cytotoxic therapy is currently the standard frontline approach for advanced endometrial cancer.

Table 6.1 First-line single-Agent chemotherapy in endometrial cancer

Drug	Dose	RR (%)
Cisplatin	50–100 mg/m^2	20–42
Carboplatin	360–400 mg/m^2	24–32
Cyclophosphamide	666–1,200 mg/m^2	0–14
Docetaxel	35–70 mg/m^2	21–31
Doxorubicin	50–60 mg/m^2	19–37
Epirubicin	80 mg/m^2	26
Etoposide, oral	50 mg	14
Liposomal doxorubicin	40 mg/m^2	12
Hexamethylmelamine	280 mg/m^2	9
Ifosfamide	1.2–5 g/m^2	12–25
Paclitaxel	210–250 mg/m^2	36–60
Methotrexate	40 mg/m^2	6
Topotecan	0.8–1.5 mg/m^2	20
Vinblastine	1.5 mg/m^2	12
Vincristine	1.4 mg/m^2	18

Data adapted from Obel et al. [3]

Reported response rates to various combinations range from 30 to 75 % with median remission durations of 6–12 months (Table 6.2) [13]. In the early 1990s, two randomized trials (see Table 6.2) showed improved response rates (over 40 % versus 25 % or less) and progression-free survival with the addition of cisplatin to doxorubicin therapy. Despite increased toxicity and tvhe lack of a clear survival benefit, doxorubicin/cisplatin-based therapy became the standard.

The feasibility of triplet chemotherapy regimens was tested in GOG 177, which was published in 2004. This phase III trial investigated the tolerability and efficacy of paclitaxel when added to the cisplatin/doxorubicin doublet. Filgrastim support was universally administered to avoid unacceptable bone marrow suppression. The three-drug regimen produced a superior response rate (57 % versus 34 %), PFS (median, 8.3 versus 5.3 months), and OS (median, 15.3 versus 12.3 months; $P = .037$). This triplet therapy became the only treatment shown to establish a survival benefit beyond results achieved with traditional doublet chemotherapy. However, the paclitaxel regimen produced significant neurotoxicity (≥ grade 2 in 39 % of patients) and required patients to come in on three successive days due to the recommended splitting of paclitaxel and doxorubicin and cisplatin treatments in an attempt to minimize cardiotoxicity and neurotoxicity. These

Table 6.2 Combination chemotherapy in chemotherapy-naïve endometrial cancer

Trial	Regimen	# of pts	RR (%)	Median OS (month)
Thigpen et al. [5]	DOX 60 mg/m^2 q 3 weeks	132	22	6.7
	DOX 60 mg/m^2+ CTX 500 mg/m^2 q 3 weeks	144	30	7.3
Pawinski et al. [6]	CTX 1,200 mg/m^2	29	14	
	IF 5 mg/m^2 q 3 weeks	32	25	
Gallion et al. [7]	DOX 60 mg/m^2 + CDDP 60 mg/m^2 q 3 weeks (circadian)	169	46	11.2
	DOX 60 mg/m^2 + CDDP 60 mg/m^2 q 3 weeks	173	49	13.2
Aapro et al. [8]	DOX 60 mg/m^2 q 4 weeks	87	17	7
	DOX 60 mg/m^2 + CDDP 50 mg/m^2 q 4 weeks	90	43	9
Thigpen et al. [9]	DOX 60 mg/m^2 q 3 weeks	131	42	9.2
	DOX 60 mg/m^2 + CDDP 50 mg/m^2 q 3 weeks	132	22	9
Fleming et al. [10]	DOX 60 mg/m^2 + CDDP 50 mg/m^2 q 3 weeks	157	40	12.6
	DOX 50 mg/m^2 + PTC 150 mg/m^2/24 h + G-CSF	160	43	13.6
Fleming et al. [11]	DOX 60 mg/m^2 + CDDP 50 mg/m^2 q 3 weeks	129	34	12.3
	DOX 45 mg/m^2 + CDDP 50 mg/m^2 + PTX 160 mg/m^2 + G-CSF	134	57	15.3
Miller [12]	PTX 175 mg/m^2 + CPL AUC 6 q 3 weeks	663	51	36.5
	DOX 45 mg/m^2 + CDDP 50 mg/m^2 + PTX 160 mg/m^2 + G-CSF	532	51	40.3

IF ifosfamide, *DOX* doxorubicin, *CTX* cyclophosphamide, *CDDP* cisplatin, *PTX* paclitaxel, *CPL* carboplatin, *EORTC* Eastern Cooperative Oncology Group, *GOG* Gynecologic Oncology Group, *G-CSF* granulocytic colony-stimulating factor

factors limited widespread adoption of the regimen, and instead, carboplatin/paclitaxel, which produced good response rates in a number of phase II trials and was already widely used for ovarian cancer, became commonly used. A recent study with weekly paclitaxel and carboplatin in chemotherapy-naive and pretreated populations showed partial response rates of 50 and 39 %, respectively [14]. The GOG therefore conducted a large non-inferiority trial comparing carboplatin and paclitaxel (TC) to paclitaxel/cisplatin/doxorubicin (TAP) in approximately 1,300 women with advanced or recurrent endometrial cancer which has been reported in abstract form. Both regimens were repeated every 21 days for a maximum of seven cycles. Half of the patients in each arm had objective responses and 30 % had stable disease. Both arms had equivalent response rates for those patients with measurable disease (51 %), and neither progression-free survival nor median overall survival differed significantly. Overall survival was shown to be 40 months with TAP and 36 months with TC. With regard to toxicity, the TAP arm had significantly more thrombocytopenia, neutropenia, sensory neuropathy, nausea, diarrhea, and vomiting [12].

How Effective Is Second-Line Chemotherapy?

The efficacy of second-line cytotoxic chemotherapy remains very limited. Table 6.3 shows results of trials with standard available cytotoxic agents. Taxanes showed good activity in the days before taxane-containing therapy was the standard first-line approach [18]. Doxorubicin is one second-line treatment option based on efficacy results obtained from frontline trials. Other agents such as topotecan and gemcitabine have shown minimal efficacy in previously treated populations [19]. Novel chemotherapeutic agents continue to be investigated, and ixabepilone, a semisynthetic lactam derivative of epothilone B, produced a response rate of 12 % in paclitaxel-pretreated patients. This prompted a randomized phase III trial comparing ixabepilone to doxorubicin or paclitaxel monotherapy, the treatment choice being dependent on the patient's first-line treatment. This study unfortunately closed for futility (ref not yet available).

In an attempt to optimize the utility of chemotherapy, much effort is being made to elucidate factors which may be predictive of response to chemotherapy. GOG 209 is investigating the effect of hormone receptor status on response to chemotherapy, but results are not yet available. Investigations are also ongoing to determine whether endometrial carcinomas that overexpress or amplify topoisomerase II might show increased sensitivity to doxorubicin-based treatment. Selective overexpression of β-tubulin subtypes such as β-tubulin III (β-III) and β-V has been demonstrated to promote taxane resistance in cell lines derived from lung, ovarian, prostate, and breast cancers [20], but this has not been confirmed clinically. Microtubule inhibitors are hydrophobic in nature and are susceptible to efflux by the product of the multidrug-resistant gene (MDR-1) and multidrug resistance protein (MRP), but, again, no clinical trials have been able to predict resistance to taxanes based on expression of either of these proteins [21]. As such, selection of chemotherapy regimens remains empiric, and pooled data from several randomized phase III Gynecologic Oncology Group (GOG) trials involving standard chemotherapy regimens show no relationship between response and histology (serous, endometrioid, and clear cell) [22].

Table 6.3 Second-line single-agent chemotherapy trials in endometrial cancer

Drug	Dose	RR (%)
Cisplatin	50 mg/m^2	4
Etoposide, oral	50 mg/m^2	0
Ifosfamide	1.2 g/m^2	15
Oxaliplatin	130 mg/m^2	13.5
Gemcitabine [15]	800 mg/m^2	4
Paclitaxel	110–200 mg/m^2	27.3
Liposomal doxorubicin	50 mg/m^2	9.5
Topotecan	0.5–1.5 mg/m^2	9
Docetaxel	36 mg/m^2	7.7
Pemetrexed [16]	900 mg/m^2	3.8
Ixabepilone [17]	40 mg/^{2}	12

Data Adapted from Obel et al. [3]

Time for Something Better

There is no doubt that chemotherapies, with their well-established levels of efficacy and their predictable toxicities, do indeed form the backbone of the currently accepted management of metastatic endometrial cancers. However, it is equally important to acknowledge that benefit from chemotherapy is modest at best and that overall survival remains in the 1 year range in spite of treatment. It is important to ensure that women who undergo chemotherapy in order to control disease and to potentially prolong life do not do so at the expense of significant toxicities which adversely affect quality of life. Alternative treatments which are better tolerated and for which response is more easily predicted are vital for the development of individualized treatment algorithms.

The phenomenal advances made with regard to the understanding of cancer biology in recent years are responsible for the exponential rate at which the scientific world is able to accumulate tumor-related data of a molecular nature. These data are critical as it spurs the development of targeted agents developed to inhibit pathways considered critical in the proliferation of cancer. Such an understanding of the intracellular signaling pathways also enables the elucidation of biomarkers which can be assessed as predictors of response to treatments.

Targeting the Biology of Endometrial Cancer

It has been long recognized that endometrial carcinomas exhibit differing biologic characteristics and this observation led to the description by Bokhman of two distinct types of endometrial cancer representative of two models of tumorigenesis [23]. These have been described as type I and type II. Type I tumors comprise 80 % of endometrial carcinomas and are believed to be estrogen-driven. They are exemplified as having endometrioid histology with low grade and more often present in premenopausal women [24]. Type II tumors are archetypically of non-endometrioid histology such as serous or clear cell and are more often diagnosed in postmenopausal women. They tend to present at a more advanced stage and have a poorer prognosis at any stage relative to type I tumors of similar stage. Differences at the molecular level have been described more recently (Table 6.4). Mutations leading to aberrant functioning of the PTEN/PI3K/mTOR pathway have been noted in a large proportion of type I tumors but are rare in type II tumors. Conversely, mutations in the critical p53 gene are rare in type I tumors but present in almost all type II tumors. Knowledge of overactive or aberrant cell signaling pathways observed at high frequency in endometrial cancers forms the basis of targeted therapies.

Table 6.4 Molecular alterations in endometrial cancer

Gene alteration	Type I (endometrioid) (%)	Type II (non-endometrioid) (%)
PTEN loss	80	5
PTEN mutation	30–50	0–11
PIK3CA	30–40	20
P53 mutation	20	90
KRAS mutation	10–30	0–10
E-cadherin loss	5–50	60–90
HER-2 amplification	1	17
HER-2 overexpression	3–10	32
β-catenin mutation	15–50	0
Microsatellite instability	15–25	0–5

Data adapted from Westin and Broaddus [25]
PTEN phosphatase and tensin homolog deleted on chromosome 10, *PIK3CA* phosphatidylinositol 3-kinase catalytic, *HER* human epidermal growth factor receptor

Hormonal therapy may be considered as the "original targeted therapy." Evidence suggesting a central role for estrogen in the development of type I endometrial cancers made hormonal therapy an excellent candidate for proposed treatment of such disease. Because the uterine endometrium is sensitive to progesterone and estrogen, and because unopposed estrogen is a strong risk factor for the development of uterine cancer, hormone therapy traditionally played a significant role in the treatment of advanced endometrial carcinoma [26]. Advanced endometrial cancer patients with no prior chemotherapy have demonstrated response rates of 20–30 % to progestin-based therapies in a number of published studies (see Table 6.5). Some studies suggest that hormonal therapy is more likely to be beneficial in a selected population of patients with low-grade tumors that are estrogen and progesterone receptor-positive [39]. Grade 3 or poorly differentiated tumors infrequently respond to hormone therapy, and chemotherapy remains the generally preferred treatment for patients with metastatic, high-grade tumors [40]. However, it is inappropriate to categorically rule out hormonal therapy options in patients whose tumors do not express high levels of hormone receptor. ER and PR status remains a very imperfect predictor of response rates to hormonal therapy in this disease, and an 8–17 % objective response rate in women with hormone receptor-negative tumors has been reported [41]. Megestrol acetate 160 mg/day is the most commonly used progestin in the United States for the treatment of endometrial carcinoma. Dose

Table 6.5 Hormone therapy in advanced endometrial cancer

Authors	Drug	*N*	RR (%)	Median OS (mos)	Prior chemotherapy
Lentz et al. [27]	MGA 800 mg/day	54	24	7.6	No
Thigpen et al. [28]	MPA 200 mg/day	145	25	11.1	No
	MPA 1,000 mg/day	154	15	7.0	
Thigpen et al. [29]	TAM 40 mg/day	68	10	8.8	No
Whitney et al. [30]	MPA 200 mg/day every other wk and TAM 40 mg/day	61	33	13	No
Fiorica et al. [31]	MGA 160 mg/day × 3 weeks followed by TAM 40 mg/day × 3 weeks	61	27	14	No
Pandya et al. [32]	MGA 160 mg/day	20	20	12.6	No
	MGA 160 mg/day + TAM 20 mg/day	42	19	8.6	
McMeekin et al. [33]	Arzoxifene 20 mg/day	29	31	13.9	No
Covens et al. [34]	Leuprolide 7.5 mg q 28 days	25	0	6	Yes (two patients)
Lhomme et al. [35]	Triptorelin 3.75 mg q 28	28	8.7	7.2	Yes
Asbury et al. [36]	Goserelin 3.6 mg q day	40	11	7.3	Yes (one patient)
Rose et al. [37]	Anastrozole 1 mg/day	23	9	6	No
Ma et al. [38]	Letrozole 2.5 mg/day	28	9.4	6.7	Yes (adjuvant)

TAM tamoxifen, *MGA* megestrol acetate, *MPA* medroxyprogesterone acetate, *Mos* months

escalation to 1,000 mg/day did not improve median overall survival or response rates [27, 28]. Tamoxifen, a selective estrogen-receptor modulator (SERM), binds to estrogen receptors and produces both estrogenic and antiestrogenic effects, depending on the target tissue. Tamoxifen has been widely used in the treatment of breast cancer (it appears to primarily act as an antiestrogen in breast tissue), and in breast cancer trials, it causes a fourfold increase in the number of uterine cancers in postmenopausal women with an intact uterus (presumably because it acts as an estrogen agonist in endometrial tissue) [42]. Interestingly, single-agent tamoxifen has shown modest single-agent antitumor activity in the setting of metastatic endometrial cancer with a reported response rate of 10 %. A third-generation SERM, arzoxifene, produced a response rate of 31 % (1 CR and 8 PR) in tumors selected for low grade (1 or 2) or hormone receptor positivity [33]. Combinations of tamoxifen and progestins were tried based on the hypothesis that resistance to progestin therapy developed because of downregulation of progesterone receptors with progestin therapy and the fact that progesterone receptors could be upregulated by tamoxifen. Whitney et al. explored the relationship between the expression of centrally determined hormone receptor expression and response to a regimen of daily tamoxifen 20 mg twice daily and intermittent medroxyprogesterone acetate 100 mg twice daily on even weeks in 45 patients. The response rate overall was 33 % [30]. In this trial, the ER H score derived by immunohistochemical evaluation using monoclonal antibody to estrogen-receptor protein was significantly related to both response and overall survival, while there was no statistically significant correlation of PR with clinical response. In a subsequent phase II trial, the GOG tested the use of megestrol acetate 80 mg twice daily for 3 weeks alternating with tamoxifen 20 mg twice daily for 3 weeks in 56 women with advanced endometrial carcinoma who had not received prior chemotherapy or hormonal therapy. The overall response rate was 27 %, median progression-free survival was 2.7 months, and median overall survival was 14 months [31]. Aromatase inhibitors including letrozole and anastrozole have been investigated but showed response rates of less than 10 % [37, 38, 43]. One small trial testing the use of letrozole found no relationship between expression of centrally assayed ER or PR and response to therapy [38]. GnRH receptors have been identified on endometrial cancers, but most studies evaluating GnRH agonists have shown limited efficacy [35, 36, 44]. Benefit from hormonal therapy appears to be sequence dependent with patients receiving hormonal therapy after chemotherapy demonstrating poor response rates. A recent trial randomized women with 1–2 prior chemotherapy regimens to the mTOR inhibitor, ridaforolimus, or progestin therapy (with medroxyprogesterone 200 mg/day or megestrol 60 mg/day), and the response rate in the progestin therapy arm was only 4.3 % [45].

In vitro and nude mouse data have suggested that inhibiting the PI3K/AKT pathway reverses progestin resistance in endometrial cancer [46]. Recent results in breast cancer have shown that acquired resistance to hormonal therapy, both tamoxifen and exemestane, can be overcome by mTOR inhibition (exemestane/everolimus [47] and tamoxifen/everolimus [48] and tamoxifen/sirolimus [49] studies). In a phase III trial, 724 patients previously treated with nonsteroidal aromatase inhibitors with postmenopausal hormone-receptor-positive advanced breast cancer were randomized to combined everolimus and exemestane versus exemestane and placebo. At the interim analysis, the combination group demonstrated a median progression-free survival of 6.9 months compared to 2.8 months with exemestane plus placebo [47]. Unfortunately results in endometrial cancer to date have been less definitive. A phase II open-label single-arm study of the combination of everolimus and letrozole enrolled 28 patients who had received 1–2 prior chemotherapy regimens and showed a promising objective response rate of 21 % [50]. The GOG conducted a randomized phase II trial, GOG-0248, testing temsirolimus 25 mg IV weekly versus the combination of temsirolimus 25 mg IV weekly plus megestrol acetate 80 mg twice daily for 3 weeks alternating with tamoxifen 20 mg twice daily for 3 weeks. Unfortunately, the combination of temsirolimus with megestrol acetate/tamoxifen resulted in an unacceptable rate of venous thrombosis (7 events out of 22 patients), and the combination arm was closed to accrual after the first stage. The preliminary results indicated a 14 % partial response rate (3 out of 21 eligible patients) and no evidence of venous thrombosis in the single-agent temsirolimus arm [50, 51]. Publication of molecular marker data from these studies that may show subsets of patients most likely to benefit is awaited, but the addition of an mTOR inhibitor to hormonal therapy does add toxicity, such as hyperglycemia, asthenia, and mucositis.

While a few patients undoubtedly have major responses to hormonal therapy, the number is not large and median progression-free survival on trials of hormonal therapy is short. Newer targeted agents have thus far not been definitively demonstrated to increase sensitivity to hormonal therapy. The inability to select which patients benefit from therapy and the short overall progression-free survival reported in trials of hormonal therapy has dampened enthusiasm for first-line use of hormonal therapy. Indeed, a Cochrane database review found insufficient evidence that adjuvant hormonal therapy as a single-agent or as a combination treatment prolonged overall or 5-year disease-free survival in women with advanced or recurrent endometrial cancer [52].

Additional targeted agents have been investigated within the context of metastatic endometrial cancers. As with hormonal therapies, they are selective for a molecular receptor

present on a large proportion of endometrial cells and postulated to be central to regulation and proliferation mechanisms which are implicated in the survival of cancer cells.

The significant proportion of PTEN and PI3K mutations observed in type I endometrial cancers has implicated the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway in the development of endometrial cancer. This pathway is involved in cellular growth regulation, proliferation, motility, survival, protein synthesis, and transcription. It is considered to be a crucial checkpoint which when malfunctioning is implicated in tumorigenesis [53]. A series of intracellular proteins form the intracellular cascade of this pathway and include PTEN, PI3K, AKT, and mammalian target of rapamycin (mTOR). Mutations within any one of these proteins ultimately lead to the constitutional activation of mTOR, and drugs inhibiting the function of one or several of the proteins implicated in this pathway have been developed in the hope that inhibition of this cellular pathway will have cytotoxic capability.

Temsirolimus, an ester of the macrocytic immunosuppressive agent sirolimus (rapamycin), is a cytostatic cell cycle inhibitor with antitumor properties. It inhibits mTOR, a serine–threonine kinase involved in the initiation of mRNA translation and has demonstrated activity in several tumor types including renal cell carcinoma where it demonstrated improved progression-free survival and overall survival when compared to interferon alfa [54]. The scientific rationale for treating endometrial cancer with mTOR inhibitors led the NCIC CTG clinical trials group to assess the activity of temsirolimus in women with recurrent or metastatic endometrial cancer. Two single-arm phase II studies were conducted differentiating between chemo-naïve and chemotherapy-exposed patients receiving temsirolimus. The combined results of these trials were published by Oza et al. [55]. Of 29 evaluable chemo-naïve patients, four (14 %) demonstrated a confirmed partial response of 5.1 months median duration (range 3.7–18.4 months) and 20 (69 %) had stable disease with a median duration of 9.7 months (range 2.1–14.6 months). Only five patients (18 %) progressed while on treatment. Of the 25 patients previously exposed to chemotherapy, only one (4 %) had a partial response to treatment while 12 (48 %) showed stabilization of disease for a median duration of 3.7 months. The observation that activity rates vary significantly based on previous treatment status should be incorporated into the design of future studies in the knowledge that better efficacy is likely to be noted in chemo-naïve individuals. The proportion of women progressing while receiving temsirolimus was lower than has been seen in trials with chemotherapy, and hormonal therapy and ongoing investigations will assess further the patient-centered relevance of disease stability due to temsirolimus. These encouraging results have led to additional trials combining temsirolimus with other chemotherapy, hormonal, or targeted agents. The interim report of a study combining temsirolimus with bevacizumab at first recurrence was presented at ASCO this year. While 20 % of patients had an objective response to treatment and a further 20 % had stable disease, prespecified efficacy assumptions were not met. These results were in contrast to those obtained with the same combination in the context of second-line therapy [56].

Kollmannsberger et al. recently reported activity of temsirolimus in combination with carboplatin and paclitaxel in a phase I study [57]. A dose-expansion cohort suggested promising activity in women with recurrent endometrial and ovarian cancer. This combination was incorporated into a randomized phase II investigation of the GOG, GOG 86P, which randomized women with chemotherapy-naïve advanced or recurrent disease to carboplatin/paclitaxel/temsirolimus followed by temsirolimus maintenance, carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance, or carboplatin/ixabepilone/bevacizumab followed by bevacizumab maintenance. This trial has completed accrual, and results are awaited.

Two additional rapamycin analogs have shown activity in endometrial cancer patients. Ridaforolimus was administered to previously treated women with metastatic endometrial cancer. Primary endpoint was defined as clinical benefit response defined as a complete or partial response or prolonged stable disease of at least 16 weeks duration. Initial results showed a clinical benefit response of 35 % [58], and clinical development of ridaforolimus continues. In addition, the results of a trial comparing ridaforolimus with hormonal or chemotherapy treatments were presented at the International Gynecologic Cancer Society meeting in 2010 and demonstrated significant advantage for ridaforolimus with a hazard ratio of 0.55. An oral formulation mTOR inhibitor everolimus has similarly shown activity warranting additional development demonstrating a 21 % confirmed clinical benefit at 20 weeks of therapy [59].

Importantly, the mTOR inhibitors have proven to be reasonably well-tolerated agents. Most of the toxicity observed has been of grade I or II severity and consists largely of fatigue, rash, mucositis, and pulmonary interstitial pneumonitis. Hyperglycemia is an issue especially in poorly controlled diabetics. The majority of the pneumonitis is asymptomatic with only a small proportion requiring pharmacologic steroid administration. NCIC data found toxicity rates to be somewhat higher in previously treated patients, and this information may ultimately be factored into decisions relating to optimal treatment sequencing. The tolerability of these convenient agents is highly relevant when considering treatment options for the average endometrial cancer patient given their relatively older age and frequent comorbidities and obesity and fuels the argument that non-chemotherapy treatment options are of huge significance in this population.

The high observed rate of PTEN loss in endometrial tumor tissue led to the belief that mTOR inhibition would be effective in this cohort. Extensive correlative studies assessing the archival tissue from the time of diagnosis of women participating in the NCIC studies have been performed. These assessed via immunohistochemistry techniques and mutational analyses the presence of PTEN, mTOR, AKT, and pS6 mutational loss [60]. PTEN loss was observed in over 60 % of women with previously untreated disease and in 40 % of previously treated women. Despite the high frequency of noted mutations in both PTEN and other implicated proteins in the pathway, disappointingly, no correlation has been demonstrated between mutations and response to mTOR inhibition. Likewise, no correlation has been observed between histologic subtype and response to mTOR inhibition. This is despite predictions that endometrioid-type disease, which harbors the highest number of alterations in the PI3K/mTOR pathway, would benefit most from mTOR inhibitors. Elucidation of an accurate predictor of response remains a crucial aim in the path towards achieving individualized cancer treatments, and all future trials must continue to focus on the incorporation of tissue sampling and well-designed correlative studies as a fundamental part of study design.

The current lack of understanding regarding predictors of response to mTOR inhibitors highlights the intricacy and the complexity of intracellular signaling pathways and the potential feedback mechanisms and protein interplay which may be responsible for the apparent lack of correlation between loss of PTEN function and response to therapy. This fact, as well as the presence of mutations in other critical proteins in the PI3K/AKT/mTOR pathway, has led to the development of different types of inhibitors. These include PI3K inhibitors as well as dual catalytic site inhibitors which may be superior to mTOR inhibitors or alternatively when administered in combination with mTOR inhibitors may provide tolerable therapies which have more substantial tumoricidal potential [61]. Trials are ongoing with several such novel agents, and once again, information from correlative studies will be essential to allow increased and in-depth understanding of mechanism of action.

How Important Is Targeting of Angiogenesis in Endometrial Cancers?

Angiogenesis has long been known to be critical to tumor development, and correlations between vascular endothelial growth factor (VEGF) expression and clinical and prognostic factors have been observed. Several publications have shown correlation between clinical stage, grade, and prognosis in VEGF receptor overexpressing tumors [62]. Bevacizumab is a well-recognized recombinant, humanized monoclonal antibody directed against VEGF. Two partial responses and five stabilizations of disease were observed in a small retrospective analysis of heavily pretreated endometrial cancer patients [63]. This led to the GOG-229-E phase II study which treated 56 previously treated patients with 15 mg/kg of bevacizumab (every 21 days) with results showing one complete and seven partial responses totaling an overall response rate of 15 % [64]. Several resulting combination trials including GOG 86P as discussed above are currently accruing in order to assess the potential benefit of the addition of bevacizumab to chemotherapy or targeted therapies. Sunitinib, a multiple tyrosine kinase inhibitor, is a second targeted agent with antiangiogenic activity to have shown promise in the treatment of endometrial cancer patients. As published in 2010 by Correa et al., sunitinib elicited 3 partial responses (15 %) and five durable stabilizations of disease demonstrating an encouraging median overall survival of 19 months [65].

Conclusions

Chemotherapy has traditionally formed the backbone of treatment for advanced endometrial cancer. The quantity and quality of evidence-based data relating to the use of chemotherapy in endometrial cancer confirms its utility while highlighting its limitations. Response rates averaging 40 % for combination regimens and a median overall survival of only 1 year for women with advanced disease leave the oncology community in no doubt that additional treatment options are urgently required. In addition, when considering the demographic characteristics of women in this cohort, the median age of presentation of 65 years, and the high rate of obesity and active diabetes, it becomes evident that alternatives to chemotherapy, if demonstrably better tolerated, would be advantageous for patients from a quality of life standpoint even if data confirming superior efficacy was lacking.

Hormonal therapy, with its preferential toxicity profile, remains a valid treatment option for women diagnosed with endometrial cancer. It is particularly attractive for those women who are unable or unwilling to tolerate chemotherapy and for whom a higher likelihood of response is predicted. With our increased ability to perform correlative studies, older and outdated studies should be revised in an attempt to better characterize those tumor types which will predictably gain benefit from hormonal therapy. Prediction of response remains the key factor in the optimization of treatment choice.

Targeted therapies, in particular mTOR inhibitors, have shown promising activity with tolerable toxicity profiles. Phase III studies are crucial to confirm this initial data and ultimately ascertain the level of activity of these agents when compared to standard chemotherapy. Given the difficulties associated with chemotherapy administration

in this population, proof of non-inferiority would be of considerable importance in establishing an active alternative to chemotherapy.

Future clinical trials whether for conventional chemotherapy agents, hormonal therapies, or highly selective targeted therapies need to incorporate well-designed correlative studies and novel clinical endpoints in order to accommodate for the gradual conceptual shift from a "one-fit-all" treatment approach to the more sophisticated goal of "individualized care." With this new paradigm of care, we must be cautious not to disregard obviously active treatment options due to logistic limitations and an inability to adapt our evidence-based methods to fit the ever-increasing number of novel agents underdevelopment. Novel agents give the opportunity for sequential rather than alternative therapy, and their availability will likely allow for improved patient-centered decision making as well as probable improvements in progression-free and overall survival.

Concluding Comments

- Targeted agents offer a potential alternative to current standards based on preliminary data demonstrating efficacy and manageable toxicity.
- Targeted agents demonstrating clinical promise must be directly compared with both conventional chemotherapy and hormonal therapy approaches in order to allow for their appropriate and optimal incorporation into clinical practice.
- Incorporation of well-designed correlative studies into future studies is paramount if treatment algorithms are to be more accurately tailored to specific patient subpopulations.

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Is Cervix Cancer a Disappearing Disease? Impact of HPV Vaccination in Developed Countries

7

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Summary Points

- Although it may be several years before the full effect of HPV vaccination on rates of cervical cancer is observed, earlier effects on high-grade abnormalities and invasive cancer rates in younger women (<40 years) are expected.
- Cervical screening will continue to be required in the foreseeable future but is likely to need to be adapted to account for HPV vaccination.
- Primary HPV screening is a promising approach, but several issues with its implementation could be clarified in pilot or sentinel site implementation.
- Monitoring the long-term effects of HPV vaccination will be important, but data are likely to be obtained from a few key countries.

Introduction

The total worldwide burden of cervical cancer in 2008 has been estimated at 530,000 new cases and 275,000 deaths per year [1]. It is now well established that infection with oncogenic human papillomavirus (HPV) is the causal factor in the development of cancer of the cervix and HPV has a role in several other cancers of the anogenital area and head and neck in both males and females [1]. HPV types 16 and 18 together account for approximately 70 % of cervical cancer globally, with the remainder accounted for by a mix of other oncogenic types. HPV vaccination, introduced in many developed countries over the last 5–6 years, has involved administration of vaccines against HPV 16 and 18 to preadolescent females. Two first-generation prophylactic vaccines are currently available – a bivalent vaccine (HPV 16/18, Cervarix™ GlaxoSmithKline) [2] and quadrivalent vaccine (HPV 16/18/6/11, Gardasil, Merck Inc, Whitehouse Station, NJ) [3]. The additional HPV types 6 and 11 included in the Gardasil vaccine are considered low risk with respect to cancer but are implicated in approximately 90 % of anogenital warts, and thus Gardasil has a spectrum of effects in the prevention of both cancer and of warts. HPV vaccination is most effectively delivered to girls aged 12–13 years or before the majority commence sexual activity, since current-generation vaccines do not act to increase clearance of existing HPV infections, and thus vaccination is unlikely to change the subsequent type-specific risk of developing a precursor lesion to invasive disease (cervical intraepithelial neoplasia grade 3, CIN3) or invasive cervical cancer in females already exposed and DNA positive for a particular HPV type [4].

The introduction of HPV vaccination into many developed countries over the last 5–6 years has been supported by modeled evaluations of cost-effectiveness. A recent systematic review identified a large number of published cost-effectiveness evaluations of female HPV vaccination in developed countries, with multiple evaluations reported in several countries [5]. Although the absolute value of the incremental cost-effectiveness ratio (ICER) varied considerably in some cases, virtually all cost-effectiveness evaluations found female vaccination was cost-effective compared to the local willingness-to-pay (WTP) threshold. Furthermore, the price at which the vaccine is supplied within many government programs may now be lower than the vaccine price considered in initial evaluations, and thus it is likely that HPV vaccination of young females is cost-effective in most countries, even in the context of established cervical screening program [5].

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Because HPV infection is causally responsible for virtually all cases of invasive cervical cancer and also has a role in several other cancers, vaccination against HPV has the potential to be one of the most effective cancer control strategies ever implemented. However, a number of factors may limit the immediate impact of HPV vaccination. These include (1) the incomplete protection against invasive cervical cancer afforded by current-generation vaccines; (2) the somewhat lower population coverage rates for vaccination achieved in some countries, which is partly due to the targeting of the HPV vaccine to preadolescents, such that it cannot be incorporated into existing childhood immunization schedules (e.g., three-dose coverage rates in the USA are estimated at 32 % in 13–17-year-old girls [6], compared to 84 % in 12–13-year-old girls in England [7] and 73 % in 12–13-year-old girls in Australia) [8]; (3) the considerable challenges in relation to the affordability of vaccines and development of the infrastructure to deliver vaccination to preadolescents in low-resource settings; (4) the need to vaccinate young females two to three decades before they will reach their peak risk of developing invasive cervical cancer; and (5) the competing effects of population aging, which will tend to increase the number of cervical cancer cases diagnosed over the next few decades, in both developed countries and low-resource settings. Because of these issues and despite the fact that the implementation of HPV vaccination has been supported by extensive clinical effectiveness data and has been shown to be a very cost-effective addition to current prevention regimens, there will be an important ongoing role for cervical screening.

The recent introduction of prophylactic HPV vaccination has been performed in the context of high levels of cervical screening in many developed country settings, either delivered through mature organized cervical screening programs or in an opportunistic manner. International evidence-based recommendations for cervical screening have been formulated and published as International Agency for Research on Cancer (IARC) recommendations [9]. These recommendations specify that the optimal interval for cytology is three years in women less than 50 years of age and 5 years in women aged 50–64 years and that the optimal age of starting screening is 25 years. However, in practice, the recommended screening interval, age of starting, and methods of organization differ markedly across settings. The recommended age to start screening varies – for example, it is 18–20 years in Australia, 23 years in Sweden, 25 years in England, and 30 years in the Netherlands and Finland. At the same time, vaccination programs have also varied in the oldest age of female included in the catch-up programs – for example, this is 18 years in England, 20 years in New Zealand, and 26 years in Australia and the USA. The relative ages of starting screening and of catch-up vaccination will be of major importance in determining the timing at which vaccination and screening are expected to interact; in countries with a younger age of starting screening and older cohorts included in vaccination catch-up (e.g., Australia), a more rapid interaction is expected.

To date, because of the relative difference in age of vaccinated and screened cohorts, HPV vaccination has not had a major direct effect on the activities and outcomes of organized screening. However, vaccination has been introduced into a cervical screening environment that to some extent is already primed for change following the completion of several major trials of primary HPV DNA screening [10–14] and the introduction of HPV as a triage and/or a test-of-cure test within many cytology-based screening programs. The advent of vaccination is likely to provide further impetus to the evolution of cervical screening recommendations in many countries. In general terms, this evolution involves the introduction of new screening technologies, especially primary HPV DNA testing, and the formulation of new recommendations for less frequent screening in a more targeted age group of women at risk of invasive cervical cancer.

Although the current review focuses on developed countries, it should be noted that in low-resource settings, the affordability and delivery of HPV vaccines are major challenges. In November 2011, the Global Alliance for Vaccines and Immunization (GAVI) announced that it would support the delivery of HPV vaccine to the lowest resource, GAVI-eligible countries. In 2013 it was announced that Merck will supply vaccine at $4·50 per dose and GSK at $4·60 per dose, and GAVI will co-finance the vaccine in the lowest resource countries [15]. However, delivery of HPV vaccine to younger cohorts will not avert the very substantial burden of disease in women already exposed to HPV, and therefore the optimal strategy would involve a combination of vaccine delivery with screening using an appropriate modality at least once or twice per lifetime for older cohorts. Historically, there has been great difficulty in establishing screening programs in low-resource settings, due both to logistical difficulties, including establishing infrastructure requirements and also developing consistent high-quality delivery systems. The challenges of vaccine delivery in low-resource settings are compounded by considerations of delivering screening to older women, since vaccination as a stand-alone intervention will take some years to substantially reduce the burden of cancer.

Controversial Areas

There are a number of important areas of uncertainty – and thus of some controversy – in relation to future impact of HPV vaccination in developed countries. These can be broadly divided into four categories. The first three of these are related to the question of how best to combine the new primary prevention strategy of prophylactic HPV vaccination with secondary prevention efforts in cervical screening.

The first – and perhaps most pressing – area of uncertainty is the timing of the effect of HPV vaccination on cervical screening programs and on invasive cervical cancer incidence and mortality rates in women of different age groups. A second, closely related, issue concerns the question of whether, how, and when screening programs should be adjusted to take account of HPV vaccination of younger cohorts in the population. It is not clear that currently existing screening strategies will be appropriate in vaccinated women or in populations of mixed vaccinated status. Furthermore, the recent announcement that a second-generation HPV vaccine, which will protect against up to 90 % of invasive cervical cancers is in Phase 3 trials [16], raises further complex questions about the future role of screening if the second-generation vaccine is successfully introduced on a widespread basis. It seems likely that current cytology-based screening strategies and systems will eventually be replaced in many countries with a new generation of molecular test technologies designed to detect the presence of HPV infection. As a consequence, a third major area of uncertainty is related to the implementation of HPV DNA testing as a primary screening test. Detailed management strategies for HPV-positive women and optimal systems for organizing HPV DNA-based screening programs need to be resolved before this new screening technology can be successfully implemented in population screening programs.

Fourthly, decisions about future cervical screening directions will need to be made in the context of some uncertainty about the longer-term effects of HPV vaccination on populations. Therefore, there will be a need to monitor for the longer-term effects of vaccination. Monitoring processes will need to consider the (theoretical) potential for replacement of vaccine-included types with other HPV types (although no substantive evidence suggesting such an effect has emerged to date), ongoing monitoring of vaccine safety, the long-term duration of protection against infection with vaccine-included types, and the level and duration of cross-protection for non-vaccine-included types. In addition, monitoring processes will need to consider the potential effects of vaccination on population screening behavior, since it is possible that vaccinated women could be less likely to participate in cervical screening.

Arguments For and Against

Will HPV Vaccination Take Several Decades to Have a Discernible Effect?

For

It has sometimes been assumed that it will be many decades before vaccination has a substantial impact on cervical cancer rates, based on consideration of the differential age between the optimal age for vaccination and the peak age of invasive cervical cancer. Although vaccination catch-up programs vary in their age range (usually extended to age 18 years for the first few years of the introduction of the vaccination program but in some countries extending up to age 26 years), it is expected that the population effectiveness will be decreased in catch-up cohorts because more females are likely to have experienced prior exposure to infection. In most countries, ongoing routine vaccination has been targeted at 12–13-year-old girls. This is younger than the median age of sexual debut in most populations and thus minimizes the possibility of prior HPV exposure. The peak age of invasive cervical cancer in unscreened populations is at 45 years or older but in well-screened populations may be from 35 to 40 years and older, since screening has favorably impacted the incidence of invasive cancer in older women. Therefore, at a minimum, there will be a delay of two to three decades before the most effectively vaccinated cohorts reach the age at which they would have experienced the peak age-specific rates of cervical cancer.

Modifiers

A comprehensive consideration of the issue of the timing of vaccination effect needs to consider a number of further factors. Firstly, although it is true that the peak age of invasive cervical cancer occurs about 35–40 years, nevertheless, rates of invasive cancer in women under 40 years of age are expected to decrease relatively more rapidly due to the effects of vaccination. Although this will have a moderate effect initially on overall (all ages standardized) rates of invasive cervical cancer, it will be an important phenomenon in its own right, particularly given a current focus on rates of cervical cancer in younger women [17]. It is likely that invasive cancer rates in young women will decline relatively rapidly, as soon as vaccinated cohorts enter the target age range for screening, in settings with high vaccination coverage. Preparations are underway to perform routine HPV typing for invasive cervical cancers diagnosed in women less than 30 years of age in England, which will allow tracking of the effect of vaccination, via an anticipated decline in HPV 16-/18-related invasive cervical cancers and a higher relative prevalence of cancers related to other oncogenic types.

In many countries, consideration has been or is being given to raising the starting age of cervical screening to age 25 years. In addition to the expected effect of HPV vaccination to reduce risk in this group, this is being driven by a number of other factors, including the evidence that cytological screening is of limited effectiveness in women younger than 25 years [18] and the lower relative burden of disease in this age group compared to that in older women. In England, the recommended age of starting screening was raised from 20 to 25 years in 2003, with full implementation completed by 2009. Although supported by the evidence and reinforced by independent scientific review, this decision became controversial, in part because of the death from cervical cancer of the reality television personality Jade Goody.

One of the subsequent effects was an increase in screening participation by women aged 25–34 years in 2009, particularly in previously underscreened women [19].

It is expected that the timing of the impact on cervical abnormalities in younger women will be relatively rapid, because rates of such abnormalities in the pre-vaccination era were at their highest in younger women. The precise timing of the effect of vaccination on these abnormalities will be country specific and will depend on the relative ages of starting screening and that of vaccination catch-up. In England, a vaccination-associated decline in rates of cervical intraepithelial neoplasia grade 3 (CIN3) has been predicted to start in 2015 [20]. In Australia, the decline in high-grade abnormalities is expected to commence even earlier due to the late age of vaccination eligibility and young age of screening commencement. Ecological data from Australia already provides supportive evidence of early effects of vaccination on high-grade abnormalities in women younger than 18 years of age [21]. Although these data should be interpreted with caution (since women under the age of 18 years are not recommended for routine cervical screening and the possibility of differential attendance in vaccinated versus non-vaccinated girls exists), nevertheless the observed changes are consistent with the predicted effect of the vaccination program to rapidly reduce the incidence of CIN.

It has been suggested that treatment for CIN may result in fertility complications and/or subsequent obstetric complications. No substantive evidence has been found for fertility complications resulting from treatment of the cervix [22]. Obstetric complications, in theory, might arise as a result of a mechanical weakening of the cervix after treatment [23, 24]. If treatment-related complications occur, then there would be expected to be a reduction in the obstetric complication rate after HPV vaccination. A 2006 meta-analysis of 27 studies found that both cold knife conization and large loop excision of the transformation zone were associated with a subsequently increased risk of preterm delivery and low birth weight in treated women [23]. However, a more recent study of linked data in the UK did not find an association between treatment and preterm delivery [25], raising the possibility that the prior results may have been linked to confounding factors and not to treatment per se or, alternatively, that colposcopy and treatment protocols in the UK are such that fewer complications may arise in that setting [25]. Some uncertainty therefore exists about the level of obstetric risk associated with treatment. Despite this uncertainty, HPV vaccination is expected to have a relatively rapid and important impact in reducing treatment rates and treatment-related anxiety in younger women.

Because HPV vaccination also has the potential to prevent cancers at sites other than the cervix in both males and females, its use in males is also under active consideration and has now been recommended in a few countries, including the USA and Australia. The inclusion of males in vaccination programs has the potential, via the effects of "herd immunity" to further decrease infection rates in females. However, the extent to which this will occur is predicted to be heavily dependent on the coverage rates achieved in females. All else being equal, there will be greater incremental effects of male vaccination if coverage rates in females are lower [5]. However, the decision to invest in male HPV vaccination is a complex one, with one evaluation showing that the investment would be better placed in increasing coverage rates in females, especially if coverage rates in females are low [26]. The resulting uncertainty about whether male vaccination will be implemented in a particular setting increases the uncertainty about the precise timing and extent of the effect of vaccination on cervical abnormality rates in females.

Will Existing Screening Guidelines Still Be Appropriate in the Postvaccination Era?

For

Organized cervical screening with cervical cytology has been highly successful in reducing cancer incidence and mortality in many developed countries. Although conventional cytology is associated with some subjectivity, quality control systems in many countries are highly developed, leading to more consistent and accurate performance. Many countries have now transitioned to liquid-based cytology (LBC). Although manually read LBC is not associated with substantial increase in sensitivity for detection of high grade CIN 2/3 compared to conventional cytology [27], it does have a lower unsatisfactory (inadequate) rate, which has been an important driver of its cost-effectiveness in some settings, notably in England (where the inadequate smear rates with conventional cytology were over 9 %, subsequently reducing to ~2 % after the introduction of LBC) [28]. The development of image analysis systems to assist in slide reading has introduced a further level of automation to the laboratory process, but it is not yet clear whether image-read LBC will be consistently cost-effective in all settings [29–31].

Although HPV vaccination will result in dramatic changes in the lifetime risk of invasive cervical cancer in young, effectively vaccinated, women, the risk in older unvaccinated women will remain unchanged. Women vaccinated as part of catch-up programs may have experienced prior exposure to one or more vaccine-included types and will thus be at an intermediate level of risk. Even in the case of effectively vaccinated young women, a residual risk of invasive cervical cancer will remain due to the possibility of infection and progression of one of the other oncogenic types (not 16 or 18). Preliminary findings also suggest that cervical screening will continue to be cost-effective even in cohorts that are now being vaccinated as preadolescents [32, 33]. For all these reasons, it is expected that some form of cervical screening will

be required for the foreseeable future. In countries with low-vaccine uptake or with an older age of starting screening (25–30 years), immediate changes to cytological screening programs may not be required, if the majority of women undergoing screening have not been offered vaccination. However, within a decade, vaccinated cohorts will reach the target age group for screening in many developed countries.

Modifiers

It is unlikely that existing screening recommendations will continue to be appropriate in all settings. Most obviously, the age of starting screening is likely to require review to account for the much lower lifetime risk of developing cervical cancer in younger vaccinated cohorts. The decreased risk in young women will reinforce policy decisions to raise the age of starting screening to at least 25 years, which is already supported by the evidence, even for unvaccinated women [18]. A second issue is that screening in populations with mixed vaccinated status (i.e., where some women have been effectively vaccinated against both HPV 16 and 18, some have been vaccinated in the catch-up phase with unknown effectiveness, and some women are unvaccinated) will pose unique challenges in terms of screening technologies and appropriate interval of screening. Cytology screening may become less accurate in the era of HPV vaccination, because HPV-16 appears to cause the most obviously severe cytologic abnormalities [34]. In the context of the vaccination-induced reduction in the prevalence of HPV 16 and 18 infections relative to other oncogenic types, cytology could potentially become less sensitive for detecting high-grade CIN. In addition, there is a possibility of cytology "de-training" effect, in which the decreasing prevalence of high-grade cytological abnormalities implies that cytopathologists become less accustomed to the manifestations of cytological abnormalities, which could also lead to loss of sensitivity. Automated image analysis systems have the potential to overcome some of these issues, but these have not yet been extensively validated on populations which have been exposed to HPV vaccination; this will be an important component of the future assessment of the performance of such systems.

A further consideration is that nonavalent vaccines, designed to protect against infection with the nine HPV types found in ~90 % of cervical cancers (as well as HPV types 6 and 11), are expected to be introduced within a few years. Therefore, it is possible that future cohorts of 12–13-year-old girls will be vaccinated with the second-generation vaccine and these females will be at even lower risk of developing invasive cervical cancer. In the postvaccination era, it will be important to reliably identify which women are at higher risk – whether they are unvaccinated, vaccinated in a catch-up program but with prior exposure to HPV, vaccinated with the first-generation vaccine, or vaccinated with the second-generation nonavalent vaccine. Irrespective of all these variables, current HPV status is likely to predict future risk of CIN and cervical cancer. Therefore, optimizing screening in the long term is likely to depend on an eventual transition to primary HPV screening. Cross-sectional data show increased sensitivity and more reliable and consistent performance of HPV testing across different settings [35]. Longitudinal cohort data show higher risk of the eventual development of CIN3+ in HPV-positive women (especially for HPV 16 and also for HPV 18) compared to HPV-negative women [36, 37]. Several large-scale randomized controlled trials have now also demonstrated the effectiveness of primary HPV testing compared to cytology [10–14].

Another factor potentially driving a transition to primary HPV testing is that rates of invasive cancer may have now stabilized in some countries with long established cervical screening programs [38]. This is likely to result from a combination of a residual proportion of difficult-to-reach women remaining underscreened or unscreened as well as the lower effectiveness of cytological screening to detect glandular lesions and adenocarcinoma. Although rates of squamous carcinoma have reduced substantially since the introduction of organized cervical screening programs, rates of adenocarcinoma may not have substantially declined. Thus, adenocarcinoma now forms a greater proportionate burden of cervical cancer in developed countries. For example, in Australia, the proportion of all cervical cancers that are adenocarcinomas has increased from 11.4 % in 1982 to 26.0 % in 2008 [38]. HPV 16 and 18 are implicated in the majority of adenocarcinoma tumors [39, 40], and thus primary HPV screening has potential to effectively prevent and detect glandular lesions and adenocarcinoma, which should further decrease rates of invasive cervical cancer overall.

Is a Change to Primary HPV Testing Likely to Prove Too Difficult a Transition?

For

Prior to its implementation, the cost-effectiveness of primary HPV testing will require modeled evaluation in specific settings, and this will be technically challenging because evaluation will need to be performed both in simulated unvaccinated and vaccinated cohorts. This evaluation will be associated with more uncertainty in settings without local clinical data on primary HPV testing. Commercial competition and automation of HPV test platforms is expected to drive the price of HPV testing down, but the cost-effectiveness of primary HPV screening will also depend on a range of other factors including the recommended screening interval, compliance with the recommendations, and the methods by which HPV-positive women are triaged and subsequently managed. There are several outstanding questions to be addressed with respect to management after primary HPV

testing. One possibility is to perform cytology triage testing on HPV-positive women and refer cytology-positive women to immediate diagnostic evaluation with colposcopy. However, the optimal management of HPV-positive and cytology triage-negative women requires further clarification. One option is to follow these women at either 12 or 24 months to assess whether HPV infection has persisted, and if so to triage with cytology a second time or immediately refer to colposcopy. A second alternative is to perform partial genotyping for HPV types 16/18 and/or 45 (depending on which HPV test platform is used). If systems with partial genotyping capability are used for primary screening, then women at the highest risk of developing CIN 3 in future, who are infected with one or more of these types, can potentially be immediately referred for colposcopy, whereas women positive for other oncogenic types can be further triaged with cytology or managed via further follow-up. A further option is to perform "co-testing" whereby HPV testing and cytology are performed together at the primary screening stage, and management is dependent on the combined test outcomes. Although co-testing with HPV and cytology is recommended in the USA as an option for women over the age of 30 years in context of screening every 5 years [41], the long-term predictive value of double-negative results for HPV and cytology appears to be very similar to that of a negative HPV test alone [36]. This implies that co-testing is less likely to be a cost-effective option compared to HPV as the sole primary screening test, since co-testing appears to deliver marginal benefits for an increased cost. In general terms, the relative effectiveness and cost-effectiveness of the various management options after HPV screening require detailed evaluation, which will need to be performed in each country and will need to take into account current screening practice, the proposed screening interval for primary HPV testing, costs, and other local factors.

The implementation challenges for introducing primary HPV screening within organized programs are substantial. Firstly, laboratory processes and technologies will require a complete overhaul. Workforce issues will be impacted because automated high-throughput systems for HPV testing will mean that fewer laboratory personnel will be required and those that remain will need different skills. Laboratory operations in many countries could potentially be consolidated to a few high-volume sites. The second major issue is the implementation of longer screening intervals which are likely to be required for effective and cost-effective primary screening with HPV. Maintaining effective longer interval screening without high levels of over- or underscreening will be a significant challenge. From the program perspective, one of the main challenges will be effective communication to women and cervical screening providers that longer interval screening with HPV testing is safe. Systems for organizing screening, including the timing of invitation and reminder letters, and disincentives for early rescreening will require redesigning for primary HPV screening.

Modifiers

Pilot or sentinel site evaluations will be an important mechanism to facilitate staged implementation of primary HPV screening in specific countries. These will need to be performed carefully because the laboratory workforce will require retraining, and pilots may take several years to configure and implement. One country leading the way in the implementation of HPV screening is the Netherlands, where a technical advisory group has now formally recommended transition to primary HPV screening. In England, pilot evaluations commencing in 2013 are planned at six sentinel sites, and these are intended to validate management strategies for HPV-positive women and to assess the performance of HPV screening in a "real-world" environment. In Australia, a range of longer interval screening strategies for both cytology and primary HPV screening is currently under consideration, and a pragmatic trial of primary HPV screening is planned which will recruit up to 100,000 women in the state of Victoria (K. Canfell and M. Saville, personal communication, 2013). Recent recommendations in the USA consolidate the approach to HPV screening in that country, which remains as a co-testing recommendation with both cytology and HPV in women over 30 years, at a 5-yearly interval [41].

Will Monitoring of the Long-Term Effects of Vaccination Be Required?

For

Regulatory agencies including the Food and Drug Administration in the USA, the European Medicines Agency (EMA), the UK Medicine Healthcare Regulatory Authority (MHRA), and the Therapeutic Goods Administration in Australia have reviewed both HPV vaccines, and in each case these agencies have concluded that the balance of benefits and risks associated with HPV vaccination in young females is favorable [42]. A number of systems are in place for adverse event monitoring following vaccination in various countries. Although the potential for type replacement by non-vaccine-included types has been raised as a theoretical concern, no evidence for this phenomenon has emerged, and it is thought to be unlikely since there is little evidence for interaction between types. For example, although multiple-type infections are common, it appears that the rate of coinfection can be explained by sexual behavior without the need to hypothesize competitive interaction or facilitation of secondary infection among the various HPV types [43]. Although long-term duration of vaccine protection is also a theoretical concern, vaccine trial follow-up information is now available to ~10 years, showing sustained protection over that time. Although early data suggest a potential anamnestic immune response which would greatly increase the effective duration of vaccine-conferred immunity [44, 45], it is possible that booster injections may be required at later point. If long-duration

protection is not sustained, this would have an impact on the vaccination cost-effectiveness, since the cost associated with booster injections would need to be considered; the available evidence suggests that this would substantially decrease the estimated cost-effectiveness of HPV vaccination [5].

In several countries, it is likely that the longer-term effects of vaccination will be monitored using a range of strategies. These include long-term follow-up of women in sentinel settings (such as in the Nordic countries) and monitoring of age-specific patterns of HPV prevalence – in population samples, in confirmed high-grade lesions, and in invasive cervical cancer. Future monitoring will also include examination of rates of cervical abnormalities in women who have, and have not, been vaccinated. In some countries, such as Australia and some Nordic countries, there will be the ability to individually link information on vaccination status with screening outcomes, and this will provide the most comprehensive information on the effect of vaccination on organized screening programs.

It is also possible that participation in screening, especially in young women, may change over time as a result of vaccination program implementation. Participation in screening is already closely monitored in many organized screening programs, and in many settings, it is likely that monitoring for an effect of vaccination on screening participation can be performed through existing mechanisms. However, the outcomes of such monitoring processes will need to be interpreted in light of a secular decline in participation in young women in many developed countries [46] and the more limited effectiveness of screening at young ages.

Modifiers

It is unlikely that all developed countries will implement formal postvaccination monitoring systems (other than direct monitoring of vaccine safety via usual mechanisms). However, evaluation of the impact of vaccination on noninvasive cervical lesions, and evaluation of the impact of vaccination on screening behavior, should be performed in a few key countries with capacity to link individual data on vaccination status with cervical screening behavior and outcomes. Additionally, many countries are likely to focus monitoring efforts on genotyping HPV infections in the population and in cervical disease. Genotyping samples of high-grade lesions and invasive cancers on a periodic basis will allow an ongoing assessment of the extent and timing of the depletion of HPV 16- and HPV 18-associated disease to be performed.

Conclusions and Future Directions

The current evidence supports the widespread implementation of HPV vaccination in young females in both developed countries and low- and middle-income countries. The evidence to date suggest that vaccine-conferred protection against new infection will be long lasting and the overall balance of benefits and harms of vaccination has been found by the independent regulatory bodies to be favorable. Evaluation of vaccination of preadolescent females has almost universally found it to be cost-effective, even in countries with established organized screening programs. Some benefits of HPV vaccination will be realized relatively quickly, and these include a reduction in noninvasive abnormalities in younger women.

However, although in the long term cervical cancer could become an exceedingly rare disease, it is unlikely to be eradicated in the foreseeable future. This is due to a range of factors including limited vaccination coverage rates and the time required for vaccinated cohorts to mature. Furthermore, there are some residual oncogenic HPV types not included in first-generation or even second-generation vaccines. Therefore, it is expected that secondary prevention with cervical screening will continue to be an important public health measure for many decades to come.

Screening programs will eventually need to be adapted to take account of the effects of HPV vaccination, but change may not need to be imminent in some countries – the timing of vaccination effect will be setting-specific and will depend on a range of factors including vaccination coverage and catch-up age range and a range of other local factors and policy considerations. Although a rapid transition from cervical cytology to primary HPV screening may not be required in some settings, planning for such a transition will be an important issue over the few years because the implementation of primary HPV screening will pose substantial challenges for the organization of screening. Staged introduction via pilot evaluations will play an important role in many countries. In the long term, there will need to be detailed consideration of screening requirements in cohorts offered second-generation vaccines, including possible consideration of once- or twice-lifetime HPV screening. In general terms, primary HPV screening holds considerable promise as a robust strategy for cervical screening in future populations in which some, but not all, women have been vaccinated against HPV.

Concluding Comments

- Vigilant monitoring of screening and vaccination histories in women less than 30 years with cervix cancer will be required, and HPV typing of those cancers will be an important aspect of surveillance in the post-vaccination era.
- Further consideration needs to be given to the role of HPV genotyping in routine screening with primary HPV testing.
- It will be important to have comprehensive systems for monitoring and evaluation of the effectiveness and safety of the screening programs in the first countries to switch to primary HPV screening.

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What Is the Role of Cytotoxic Chemotherapy in Advanced Cervical Cancer?

8

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Summary Points

- Adjuvant Chemotherapy after Surgery
- The Role of Neoadjuvant Chemotherapy
- Concurrent Chemotherapy and Radiation for Locally Advanced Disease
- Combining Chemoradiation and Adjuvant Chemotherapy
- The Addition of Chemotherapy to Extended Field Radiation for Patients with Known Para-Aortic Disease
- Chemotherapy for Recurrent or Metastatic Disease
- The Use of Targeted Agents

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Introduction

Cervical cancer is the second most common cancer of women worldwide, with an estimated 529,000 cases in 2009 [1] and a 5-year prevalence of more than 1.4 million cases. Cervical cancer accounted for approximately 275,100 deaths worldwide in 2009 [1] and is the leading cause of death of women from cancer in developing countries [2]. Treatment outcome and prognosis are highly dependent upon stage at diagnosis. Cervical cancer is clinically staged according to the 2009 FIGO staging system.

Stage IA1 cervical cancer is treated with conization or hysterectomy, and the vast majority of patients are cured with this approach [3]. The standard treatment for stage IA2 squamous cell carcinoma is a modified (type II) radical hysterectomy and pelvic lymphadenectomy. Stage IB is divided into IB1 (lesions less than 4 cm) and IB2 (lesions confined to cervix >4 cm). IB1 lesions can be treated with one of two different regimens. Patients can undergo radical hysterectomy and pelvic lymph node dissection followed by tailored (chemo)radiation as indicated by pathologic results, or primary radiation concurrent with chemotherapy. Both treatment options offer equivalent outcomes, and the decision to proceed with either modality is based on the patient's age, medical comorbidities, and surgical feasibility. This represents the initial opportunity for studies of the additional role of chemotherapy to the treatment paradigm of cervical cancer.

IB2 cervical cancers can either be treated with up-front surgery followed by tailored (chemo)radiation as indicated by pathologic results or chemoradiation with curative intent. A 1999 prospective, randomized Gynecologic Oncology Group (GOG) trial [4] of 374 patients with IB2 cervical cancer randomly assigned patients to be treated with radiation therapy (external beam and intracavitary cesium) and adjuvant extrafascial hysterectomy 3–6 weeks later, with or without weekly intravenous cisplatin at a dose of 40 mg/m^2 for 6 weeks during the external radiation. Residual cancer in the operative specimen was significantly reduced in the group

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receiving cisplatin, to 47 % down from 57 %. Survival at 24 months was significantly improved by the addition of cisplatin, being 89 % with and 79 % without chemotherapy. There was also a significant improvement in recurrence-free survival, from 69 % without chemotherapy to 81 % with cisplatin. Grade 3 and 4 hematologic and gastrointestinal toxicities were more frequent in the group receiving cisplatin, whereas other toxicities were equivalent in both treatment arms.

Using this data as a starting point, the role of chemotherapy in the treatment of cervical cancer has undergone a remarkable evolution over the past 15 years. In this chapter we will discuss the role of adjuvant chemotherapy after surgery, the potential use of neoadjuvant chemotherapy, the use of combined chemoradiation, adjuvant chemotherapy after chemoradiation, chemotherapy and biologic agents in the metastatic and recurrent setting, and, finally, potential future directions of treatment.

What Is the Evidence for Adjuvant Chemotherapy After Surgery?

There are limited data and few adequately powered randomized trials regarding the role of adjuvant chemotherapy after radical surgery for the treatment of cervical cancer. The Japanese Gynecologic Oncology Group randomized patients who had undergone surgery ($n=623$) or surgery and radiation therapy ($n=919$) to receive oral 5-FU for 1 year or observation. No benefit for 5-FU was seen in patients who received surgery alone. However, an improved 5-year survival was seen in patients who had surgery, radiation, and 5-FU as compared to those who received surgery and radiation alone [5]. A trial in Thailand randomized 926 patients with stage IIB–IVA cervical cancer to one of four arms: radiation therapy, radiation therapy plus adjuvant (5-FU) chemotherapy, radiation therapy and concurrent (mitomycin C) chemotherapy, and radiation therapy plus concurrent (mitomycin C) and adjuvant (5-FU) chemotherapy. The 5-year disease-free survival was 48.2, 54.1, 64.5, and 59.7 %, respectively, suggesting a benefit from adjuvant chemotherapy [6]. A recent phase II trial of 125 patients with early cervical cancer compared adjuvant paclitaxel/cisplatin (TP) chemotherapy to radiotherapy in patients who had undergone radical hysterectomy. The 3-year recurrence-free survival for chemotherapy-treated patients was 78.1 %, compared to 67.3 % for RT ($p=0.23$). The 3-year overall survival was 93.8 % with TP versus 69.4 % with RT ($p=0.02$). The authors concluded that postoperative chemotherapy using TP may have a survival benefit compared to adjuvant RT for patients with early-stage disease, along with reduced postoperative complications [7]. Japanese investigators reported similar results using adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB–IIA cervical cancer [8]. In 65 consecutive patients with stage IB or IIA cervical cancer who were initially treated with radical hysterectomy and pelvic lymphadenectomy, chemotherapy was administered using three courses of bleomycin, vincristine, mitomycin, and cisplatin for intermediate-risk cases and five courses for high-risk cases. The estimated 5-year disease-free survival was 93.3 % for the 30 patients with intermediate-risk tumors and 85.7 % for the 35 patients with high-risk tumors. These results indicate a potential role for adjuvant chemotherapy on its own for patients with cervical cancer.

Does Neoadjuvant Therapy Have a Place in the Management of Cervical Cancer?

Neoadjuvant chemotherapy (NAC) is a potential therapeutic modality prior to radical hysterectomy or radiotherapy for locally advanced cervical cancer (stage IB2, IIB, III, or IV). Neoadjuvant chemotherapy is used to reduce the tumor volume prior to radical surgery or chemoradiation. The goal of NAC is to increase the probability of complete tumor resection with free surgical margins and to optimize the safety of surgery. Additional goals are to increase the effectiveness to radiation and the early treatment of micrometastases and the prevention of distant metastases. Theoretically, NAC has the ability to not disturb the blood supply to the tumor as occurs with surgery or radiation. However, there remains the possibility of delaying the main curative treatment via radical surgery, radiotherapy, or chemoradiotherapy. There also remains the possibility of developing radioresistant cell clones. There are reports of randomized controlled trials utilizing NAC followed by surgery and radiation therapy [9]. In 2003, a meta-analysis was reported involving 872 patients from 5 randomized trials [10]. The combined results from the 5 trials indicated a highly significant reduction in the risk of death with NAC (HR = 0.65, 95 % CI = 0.53–0.80, $p=0.00004$) and also a highly significant reduction in the risk of disease progression or recurrence with NAC (HR = 0.68, 95 % CI = 0.56–0.82, $p=0.0001$). However, as the authors of this study stated, these analyses potentially suffer from selection biases and a significant amount of heterogeneity and are, therefore, inconclusive. The timing and dose intensity of cisplatin-based NAC appears to play an important role in whether or not it benefits women with locally advanced cervical cancer. This meta-analysis included radiation alone, not chemoradiation. Benedetti-Panici et al. reported on 441 patients with stage IB2–III cervical cancer who were randomized to cisplatin-based NAC followed by radical hysterectomy or external beam radiation (45–50 Gy) followed by brachytherapy [11]. The 5-year overall survival (OS) and progression-free survival (PFS) rates were 59 and 55 % for NAC and surgery and 45 and 41 % for radiation ($p=0.007$ and $p=0.02$), respectively.

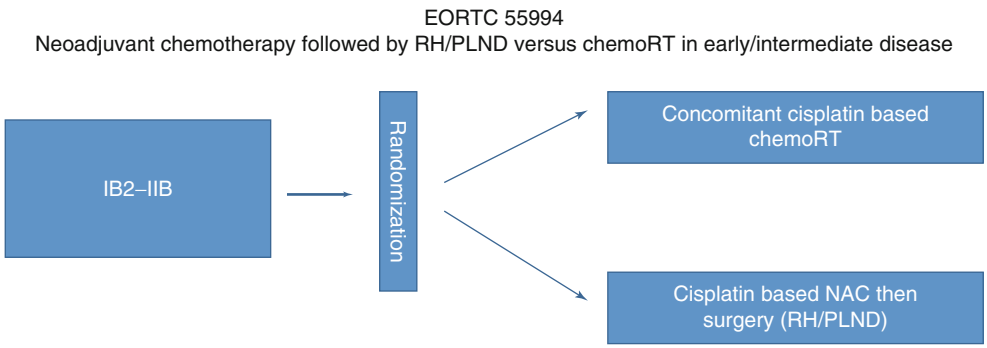

Fig. 8.1 Schema for EORTC 55994, a phase III, randomized controlled trial in patients with early-stage and intermediate-risk disease treated with neoadjuvant chemotherapy followed by either surgical management or combined chemotherapy and radiation

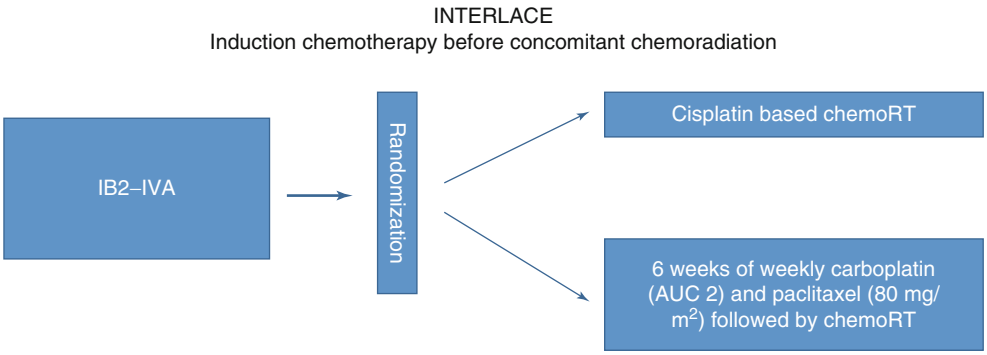

Fig. 8.2 Schema for INTERLACE, a phase III, randomized controlled trial in patients with early stage through locally advanced disease who are randomized to induction chemotherapy or no treatment before definitive combined chemotherapy and radiation

A subgroup survival analysis was undertaken in stage IB2–IIB patients. The subgroup analysis showed an OS and PFS of 65 and 60 % in the NAC and surgery arm compared to 46 and 47 % in the radiation arm ($p=0.005$ and $p=0.02$). NAC followed by radical surgery showed a significant improvement of OS and PFS in this trial. However, Chang et al. showed no significant difference in OS and PFS between NAC (cisplatin, vincristine, bleomycin) followed by radical hysterectomy and radiotherapy in patients with bulky (primary tumor ≥4 cm) stage IB or IIA cervical cancer [12]. Two randomized trials are currently evaluating the role of NAC. The first, EORTC 55994, compares NAC followed by surgery to concomitant radiotherapy and chemotherapy in FIGO IB2, IIA >4 cm, or IIB cervical cancer (Fig. 8.1). The second is a phase III trial in patients with locally advanced disease for whom surgery is not suitable. INTERLACE will compare the survival of patients treated with weekly induction chemotherapy using carboplatin and paclitaxel followed by standard chemoradiation versus standard chemoradiation alone. The trial is currently open in the UK and will include international centers (Fig. 8.2). Sardi et al. reported a randomized trial of 205 patients with stage IB disease comparing NAC (cisplatin, vincristine, bleomycin) followed by radical hysterectomy then pelvic radiation and up-front radical hysterectomy followed by adjuvant whole-pelvic radiation [13]. No statistically significant differences were seen in OS and DFS in patients with tumors with 2–4 cm in diameter, while in patients with tumors greater than 4 cm, they found significantly improved 9-year OS (80 % in the NAC group vs 61 % in the control group, $p<0.01$). There was an increased ability to achieve negative surgical margins in bulky tumors in the NAC group (61/61, 100 %) compared to the control group (48/56, 85 %; $p<0.01$). The authors concluded that NAC improved OS because of the increased ability to achieve a negative surgical margin and a decrease in pathological risk factors such as lymphovascular space invasion, parametrial invasion, and lymph node involvement in stage IB2 patients. Napolitano et al. reported on 192 patients with stage IB–IIB disease who were randomized to either NAC (cisplatin, vincristine, bleomycin) followed by surgery or control conventional surgery or radiotherapy [14]. The authors did not find a statistically significant difference in 5-year OS between the two groups with stage IB–IIA disease. However, they did report an improved 5-year DFS (77 % in the NAC group vs 64 % in the control group, $p<0.05$). Patients with stage IIB disease had no difference in either OS or DFS. In 2007, the GOG reported the results of their trial of 288 bulky stage IB2 patients who were randomized to NAC (cisplatin, vincristine) followed by radical hysterectomy and pelvic/para-aortic lymphadenectomy (RHPPL) or radical hysterectomy with lymph node dissection [15]. Adjuvant radiation therapy was prescribed for specific surgical/pathological risk factors for both regimens. The NAC group had very similar recurrence rates (relative risk, 0.998) and death rates (relative risk, 1.008) when compared to the control group. Chen et al. reported on the use of a modified NAC schema with a short burst of high-dose preoperative chemotherapy followed by surgery compared to surgery alone in 142 patients with locally advanced

cervical cancer. The authors found that on multivariate analysis, there was no survival improvement in the NAC group. However, patients who demonstrated a significant response to up-front chemotherapy had improved survival [16]. In 2006, Cai et al. reported a trial of 106 stage IB patients who were randomized to either NAC (cisplatin, 5-FU) (with or without radiotherapy) or primary surgery (with or without radiotherapy) [17]. The overall 5-year survival rate was significantly higher in the NAC group (85 %) than in the control group (76 %) ($p=0.011$). They also showed decreased rates of pelvic lymph node metastases, LVSI, and parametrial invasion in the NAC group.

While there have been a number of randomized trials examining the use of NAC in locally advanced cervical cancer, the question remains as to the efficacy of such an approach. The majority of the trials indicate a higher rate of margin-free surgery and tumor response, but this does not always translate into improved survival outcomes.

In an effort to examine the use of NAC before surgery or concomitant chemotherapy and radiation, Duenas-Gonzalez et al. performed a nonrandomized comparison of the results of two consecutive phase II studies in stage IB2–IIIB patients. The 41 patients in the NAC arm were treated with three cycles of cisplatin and gemcitabine followed by surgery or chemoradiation for inoperable cases. In a separate trial, 41 patients were treated with standard cisplatin-based chemoradiation. At a median follow-up of 28 and 24 months, respectively, there were no significant differences in PFS or OS in the NAC trial versus the standard chemoradiation trial indicating that either treatment modality may be acceptable [18]. In 2007, the Korean GOG reported a retrospective review of their experience using different treatment modalities for 692 stage IB2 cervical cancer patients treated between 1995 and 2005. They compared primary radical hysterectomy, NAC followed by radiotherapy and/or extrafascial hysterectomy, and, finally, cisplatin-based chemoradiation and/or extrafascial hysterectomy [19]. The surgery group showed the best results, with an 89 % 5-year DFS. However, there was no statistical difference between the surgery, NAC, and chemoradiation groups.

What Drugs Should Be Used for Neoadjuvant Chemotherapy?

No consensus has yet been obtained regarding the ideal, specific chemotherapy regimen for use as neoadjuvant chemotherapy. There are many reports with the PBV (cisplatin, bleomycin, vincristine) regimen that have shown a 70–80 % response rate. Recently, taxanes such as paclitaxel and docetaxel have been used in NAC regimens [20, 21]. Nagao et al. reported that docetaxel and carboplatin as a NAC regimen for patients with stage IB2–IV disease or recurrent cervical cancer had an overall response rate of 76 % (13/17). The five cases of adenocarcinoma in this cohort had a 100 % RR [20]. Yin et al. retrospectively reviewed 252 consecutive patients with locally advanced disease who were treated with NAC. In their review, 104 patients received nedaplatin and paclitaxel (NP) while the others received PC (paclitaxel and cisplatin). The patients treated with NP NAC had a higher response rate (81 %) compared with the chemotherapy regimen of PC (68 %, $p=0.0267$) [21]. The combination of a platinum and taxane agent appears to be most efficacious, but further study is required to determine the most active regimen in the neoadjuvant setting. NAC followed by surgery is thought to be superior to radiotherapy alone; however, at present, there is no compelling evidence to definitively state that NAC followed by surgery is superior to primary radical surgery alone or primary cisplatin-based chemoradiation alone.

What Is the Role for Adjuvant Chemotherapy Following Surgery?

Adjuvant pelvic radiation following radical hysterectomy is currently given for two sets of indications: firstly, for those patients whose pathology shows involved nodes, disease in the parametria, or positive surgical margins and, secondly, for those patients with negative nodes but high-risk features in the primary tumor (this indication not used universally). The Southwest Oncology Group (SWOG) and the GOG reported the results of a randomized study in 2002 of 243 patients with FIGO stages IA2, IB1, IB2, and IIA cervical cancer who were found to have positive pelvic lymph nodes, parametrial involvement, or positive surgical margins at the time of primary radical hysterectomy and pelvic lymph node dissection [22]. In order to enroll in the trial, patients had to have confirmed negative para-aortic nodes. The patients were randomized to two treatment arms. The first arm consisted of external beam whole-pelvic radiation given concomitantly with intravenous cisplatin at a dose of 70 mg/m^2 followed by a 96-h continuous intravenous infusion of 5-FU (1,000 mg/m^2). The treatment was given every 3 weeks for a total of four cycles. The second treatment arm consisted of external pelvic radiation. The radiation technique in both arms delivered 49.3 Gy to the pelvis utilizing a four-field box technique. Patients with known metastatic disease in high common iliac nodes also received 45 Gy to the para-aortic field. A statistically significant improvement in overall survival was noted in the chemoradiation arm. The reported 3-year survival rate for the 127 patients on the concomitant chemotherapy and radiation arm was 87 %, and the 116 women who were treated with adjuvant radiation alone had a 3-year survival of 77 %. The hazard ratio for overall survival was 1.96 for the patients treated with chemoradiation, and

this was a statistically significant improvement. In 2005, an update on the trial was reported [23]. In those women whose tumors were less than 2 cm, a 5-year overall survival of 82 % was noted when they were treated with concurrent chemotherapy and radiation compared to a 77 % when treated with radiation alone. This thus translated to an absolute improvement in 5-year survival for adjuvant chemotherapy of only 5 %. For those women with tumors larger than 2 cm, there was a statistically significant improvement in 5-year survival of 19 % (58 % vs 77 %). Women who were found to have only one positive node had a relatively modest, nonstatistically significant improvement of 4 % in their 5-year survival with chemoradiation, going from 79 % up to 83 %. However, when two or more lymph nodes were positive, there was a statistically significant 20 % improvement in their overall survival when treated with combined chemotherapy and radiation, going from 55 % up to 75 %. Despite the increased rates of grade 3 and 4 hematologic and gastrointestinal toxicity in the chemoradiation arm, these results established concomitant chemotherapy and radiation as the standard of care for patients in this population.

Patients with negative lymph nodes but high-risk tumor features represent a group where controversy still exists in their management. These high-risk features include size greater than 4 cm, lymphovascular space invasion, and deep stromal invasion. Women who have negative nodes have an 85–90 % survival rate after radical hysterectomy and pelvic lymphadenectomy. However, this patient population results in 50 % of treatment failures, with 70 % of the recurrences occurring in the pelvis [24]. In 1999, the GOG reported the results of a trial of 277 patients with high-risk stage IB cervical cancer who underwent radical hysterectomy and were then randomized to adjuvant whole-pelvic radiation at a dose of 50.4 Gy versus no further treatment [25]. In order to participate in the trial, patients had to have certain risk factors that placed them at a high risk for recurrence. For patients with capillary space lymphatic tumor involvement (CLS) and deep 1/3 stromal invasion, any tumor size was allowed. For patients with CLS and stromal invasion to the middle 1/3, the required tumor size was at least 2 cm. In the setting of CLS and superficial 1/3 stromal invasion, a tumor size of at least 5 cm was required for enrollment. Finally, patients without CLS were required to have deep or middle 1/3 stromal invasion and a tumor size of at least 4 cm. Patients treated with adjuvant radiation had a 15 % recurrence rate at 2 years. Those patients that were randomized to observation had a 2-year recurrence rate of 28 %, and the improvement with radiation was statistically significant. The improvement in recurrence rate came at a cost of increased toxicity. Grade 3 and 4 gastrointestinal or genitourinary toxicity occurred in 6.2 % of patients receiving radiation versus 1.4 % in the observation arm. In 2006, an update of this trial was published that included seven additional recurrences and 19 additional deaths [26]. The patients who were randomized to adjuvant radiation therapy continued to show a statistically significant reduction in their recurrence rate, but the improvement in overall survival with radiation did not reach statistical significance (HR = 0.70, 90 % CI 0.45–1.05; $p = 0.074$). GOG 263 is a phase III trial, currently open, that randomizes patients with intermediate-risk stage I/IIA disease to either RT (IMRT or standard pelvic RT) or concurrent cisplatin (40 mg/m^2 given weekly for six cycles) and RT. Patients are required to have undergone a radical hysterectomy with pelvic lymphadenectomy. The aim of this trial is to determine if there is a survival benefit for chemoradiation in patients with intermediate-risk disease.

The group from Leiden University in the Netherlands identified 51 patients who had two of the three high-risk factors identified by the GOG, among 402 patients who underwent radical hysterectomy for early-stage cervical cancer [27]. They compared 34 patients (66 %) who received postoperative pelvic radiation with 17 patients (33 %) who underwent observation. A statistically significant improvement was noted in 5-year cancer-specific survival in the group treated with pelvic radiation (86 % vs 57 %). Patients with lymph node involvement, parametrial invasion, or positive surgical margins were excluded from the study. There remains no definitive evidence that chemotherapy in addition to radiation therapy improves outcomes in patients with large tumor size, lymphovascular space invasion, and/or deep stromal invasion. Those patients with involved nodes, disease in the parametria, or positive surgical margins derive a survival benefit from concomitant chemotherapy and radiation.

Encouraging results have been reported for women with intermediate and high-risk cervical cancer treated with adjuvant chemotherapy alone following radical hysterectomy. In one report from Japan published in 2006 of 65 consecutive patients with stage IB or IIA disease, intermediate-risk disease was defined as greater than 50 % stromal invasion while high-risk disease was defined as positive surgical margins, parametrial invasion, or lymph node metastases. Three cycles of bleomycin (5 mg in 500 mL of saline administered via continuous infusion for 7 days), vincristine (0.7 mg/m^2 given on day 7), mitomycin C (7 mg/m^2 on day 7), and cisplatin (10 mg/m^2 given on day 1 through 7 over 4 h) were given for patients with intermediate-risk disease while patients with high-risk disease were treated with five cycles. Five-year progression-free survival was 93.3 % for the 30 patients with intermediate-risk tumors and 85.7 % for the 35 patients with high-risk tumors. The locoregional recurrence rate was 3.3 % in the intermediate-risk group and 8.6 % in the high-risk group. The authors of this study argued that the use of adjuvant chemotherapy alone for intermediate and high-risk cervical cancer would allow for the use of higher doses of chemotherapy than would be used with concurrent radiation and also result in lower rates of distant metastasis.

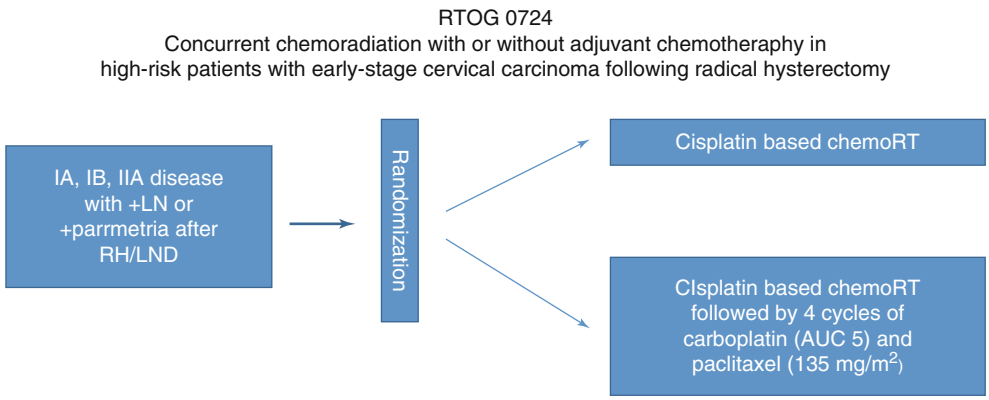

Fig. 8.3 Schema for RTOG 0724, a phase III, randomized controlled trial in early-stage, high-risk patients treated with combined chemotherapy and radiation with or without adjuvant chemotherapy

Chemotherapy alone would also incur less toxicity than concurrent chemoradiation. Additionally, pelvic radiation could then be utilized in the recurrent setting. This approach has not been validated in a prospective, randomized fashion. The RTOG currently is enrolling high-risk early-stage patients in a randomized, phase III trial comparing chemoradiation with or without adjuvant chemotherapy. High risk is defined as positive nodes or positive parametria following radical hysterectomy and the chemotherapy regimen consists of carboplatin and paclitaxel (Fig. 8.3).

Evidence for the Role of Chemoradiation Compared to Radiation Alone in the Treatment of Locally Advanced Cervical Cancer

Locally advanced cervical cancer is not effectively treated with surgery. The usual treatment in these situations is radiation. Three large randomized prospective trials reported in 1999 established concomitant chemotherapy and radiation as the treatment of choice for patients with locally advanced cervical cancer. The GOG reported the results of a phase III randomized study of external beam pelvic radiation and intracavitary radiation combined with concomitant hydroxyurea (3 g by mouth twice weekly) versus weekly cisplatin (40 mg/m^2 for 6 weeks) versus 5-FU (1,000 mg/m^2/day as a 96-h infusion on days 1 and 29)-cisplatin (50 mg/m^2 days 1 and 29) and hydroxyurea (2 mg/m^2 twice weekly for 6 weeks) [HFC] in 526 patients with stages IIB, III, and IVA cervical cancer who had undergone extraperitoneal surgical sampling of the para-aortic lymph nodes. Women with intraperitoneal disease or disease metastatic to the para-aortic lymph nodes were ineligible [28]. The median follow-up was 35 months. The two arms with platinum-containing regimens had statistically improved progression-free survival compared to the regimen with hydroxyurea alone. Seventy percent of the patients in the weekly cisplatin group and 67 % of the patients in the HFC arm were recurrence-free at 2 years. Only 50 % of the patients treated with hydroxyurea alone arm were recurrence-free at 2 years. Grade 3 or 4 hematologic and grade 4 gastrointestinal toxicities were significantly increased with HFC compared with weekly cisplatin or hydroxyurea. While both platinum-containing regimens improved outcomes compared to hydroxyurea alone in patients with locally advanced cervical cancer, the weekly cisplatin arm was better tolerated than HFC. In 2007, the authors published their long-term follow-up from the trial that confirmed the statistically significant improved outcomes with the platinum-containing regimens [29]. The relative risk of progression of disease or death was 0.57 with weekly cisplatin and 0.51 with HFC chemotherapy compared with hydroxyurea alone.

Between 1990 and 1997, the Radiation Therapy Oncology Group (RTOG) randomized 403 patients with locally advanced cervical cancer (stages IIB through IVA or stage IB or IIA with a tumor diameter of at least 5 cm or involvement of pelvic lymph nodes) between 45 Gy of pelvic plus para-aortic radiation and 45 Gy of pelvic radiation with concomitant cisplatin (75 mg/m^2 over 4 h on day 1) and 5-FU (4,000 mg/m^2 over 96 h) [30]. Para-aortic lymph nodes were evaluated by bipedal lymphangiography or retroperitoneal surgical exploration, and if positive, then the patient was excluded. At a median follow-up of 43 months, there were 193 patients in each group eligible for evaluation. There was a statistically significant improvement in 5-year overall and progression-free survival in the chemoradiation arm. The overall survival at 5 years was 73 % among patients undergoing chemoradiation compared to 58 % in the group of patients treated with radiation alone. Progression-free 5-year survival was 67 % in the chemoradiation arm and 40 % in the radiation alone arm. The rates of distal metastases and locoregional recurrences were significantly higher among patients treated with radiation alone. While there was a higher rate of acute grade 3 and 4 toxicities in the combined therapy group, these side effects were usually self-limited. Additionally, there was no significant difference in the rates of late toxicities. In 2004, an update of the trial was published. Patients with stage IB–IIB disease continued to

demonstrate a statistically significant improvement in overall survival and progression-free survival when treated with combined chemotherapy and radiation versus radiation alone. Patients with stage III–IVA disease continued to have a statistically significant improvement in their progression-free survival and a trend towards an improved overall survival. Similar to the initial publication, there were no significant differences in the toxicity profile between the different treatment arms [31].

The GOG, in collaboration with the SWOG, randomized 388 women with stage IIB, III, or IVA disease and negative para-aortic nodes based on surgical sampling to two different treatment arms. The first arm was treated with pelvic radiation with hydroxyurea (80 mg/kg given twice weekly), and the second arm was treated with standard pelvic radiation with 5-fluorouracil (4,000 mg/m^2 total dose each cycle) and cisplatin (50 mg/m^2) [32]. While the rate of severe leucopenia was higher in the hydroxyurea group, both progression-free survival and overall survival were significantly higher in the group treated with cisplatin and 5-FU in addition to radiation.

The three trials described above helped to bring about a sea change in the management of locally advanced cervical cancer. However, two other randomized trials did not show a benefit for concomitant chemotherapy and radiation in these patients. In 2002, the National Cancer Institute of Canada published their results of 259 patients with stage IB–IVA cervical SCC who were randomly assigned to external beam radiation plus brachytherapy or radiation and concurrent cisplatin (40 mg/m^2 weekly) [33]. While the 5-year survival of the patients in the chemoradiation arm was 62 % and the survival rate was 58 % in the radiation alone arm, this difference failed to reach statistical significance. In 1997, investigators from Taiwan published the results of their randomized trial of 122 patients with bulky IIB or IIIB cervical cancer [34]. Patients were randomized to treatment with pelvic radiation with or without a multi-agent chemotherapy regimen. The chemotherapy consisted of a combination of cisplatin, vinblastine, and bleomycin given on days 1 through 4 and then days 22 through 25 of the radiation course followed by two additional cycles of chemotherapy. At a median follow-up of 47 months, the arm treated with concomitant chemotherapy and radiation did not have a significant improvement in their 3-year progression-free (52 vs 53 %) or overall survival (62 vs 65 %) compared to the arm treated with radiation alone.

An individual patient data Cochrane meta-analysis, which was published in 2010, included 13 trials that randomly assigned women with cervical cancer confined to the pelvis to concurrent chemotherapy and radiation versus radiation alone following hysterectomy [35]. Combined chemotherapy and radiation was associated with a statistically significant 19 % reduction in the risk of death as compared to radiation alone. This significant decrease in the risk of death translated into an absolute improvement in 5-year survival from 60 to 66 %, a 22 % improvement in progression-free survival, and a significant decrease in both local and distant recurrence rates. Clinical benefit was demonstrated across all disease stages; however, the most dramatic survival benefit was noted in stages IA–IIA. The absolute survival improvement was 6 % and relapse-free survival improvement 8 %, and also showed efficacy of non-cisplatin-based regimens [36].

To optimize the safety and efficacy of cisplatin-based chemoradiation, two strategies are being actively investigated. The first is to increase the intensity of concurrent chemotherapy. To address this, Umayahara et al. performed a phase I study evaluating chemoradiation that included the combination of cisplatin and paclitaxel [37]. These researchers concluded that weekly administration of cisplatin 30 mg/m^2 and paclitaxel 50 mg/m^2 with definitive radiotherapy is tolerable and safe. A multi-institutional phase II study utilizing the above doses is currently under way in Japan. The second strategy is to deliver an additional systemic chemotherapy regimen in addition to concomitant chemotherapy and radiation.

The GCIG and Korean Gynecologic Oncology Group are currently investigating the effect of triweekly cisplatin delivered at a dose of 75 mg/m^2 with concurrent radiation versus 40 mg/m^2 weekly in patients with locally advanced disease in a randomized, phase III trial (Fig. 8.4). The impetus for this trial comes from a recently reported randomized, phase II study of 102 patients comparing the same treatment arms from the same group of investigators. Triweekly cisplatin was found to improve the 5-year overall survival compared

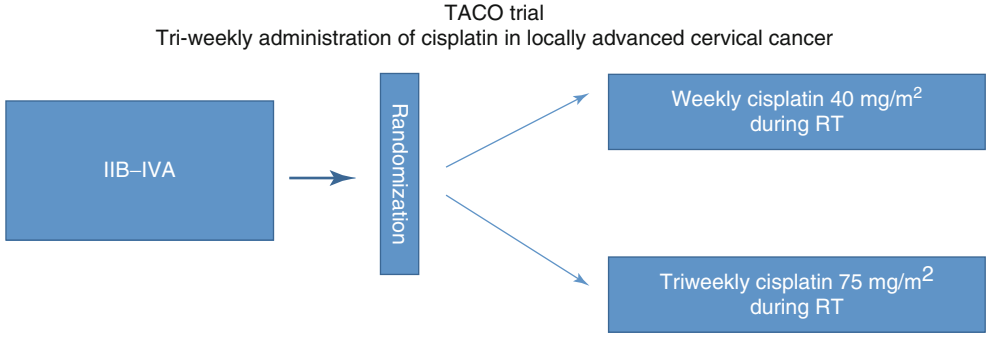

Fig. 8.4 Schema for TACO trial, a phase III, randomized controlled trial in patients with locally advanced disease randomized to receive either weekly or triweekly cisplatin as concomitant chemotherapy with radiation

to weekly cisplatin (89 % vs 66 % [$p=0.03$]). This survival improvement came with the added benefit of significantly lower rates of grade 3/4 neutropenia (22 % vs 40 % [$p<0.05$]) [38]. Treatment delivered every 3 weeks compared to weekly is, obviously, less expensive and easier to administer, and this is significant in settings where resources are limited.

Combining Chemoradiation and Adjuvant Chemotherapy

Investigators from Mexico have recently published the results of a phase III trial comparing the effect of the addition of gemcitabine to cisplatin during chemoradiation and then the addition of gemcitabine to cisplatin for adjuvant chemotherapy on PFS in patients with stage IIB–IVA disease. The experimental arm consisted of patients treated with cisplatin 40 mg/m^2 and gemcitabine 125 mg/m^2 weekly for 6 weeks with concurrent external beam radiotherapy (50.4 Gy in 28 fractions), followed by brachytherapy (30–35 Gy in 96 h), and then two adjuvant 21-day cycles of cisplatin (50 mg/m^2 on day 1) plus gemcitabine (1,000 mg/m^2 on days 1 and 8). The control arm consisted of patients treated with cisplatin and concurrent XRT followed by brachytherapy with the same dose schedule as in the experimental arm. A total of 515 patients were enrolled. Patients in the experimental arm had a significant improvement in their 3-year PFS (74.4 % vs 65.0 %, $p=.029$), but this improvement came at the expense of a dramatic increase in the rates of grade 3 and 4 toxicities (86.5 % vs 46.3 %, $p<.001$) along with two likely treatment-related deaths in the experimental arm [39].

The Australia New Zealand Gynaecological Oncology Group (ANZGOG) is currently leading the OUTBACK trial that is designed to evaluate the therapeutic value of adding an adjuvant chemotherapy regimen to standard cisplatin-based chemoradiation (Fig. 8.5). Concern has been raised regarding the additional toxicity from the additional chemotherapy and if the additive toxicity would preclude patients from receiving the appropriate treatment. A phase I study designed to determine the optimal dose of adjuvant chemotherapy will begin soon in Japan. Finally, the third strategy is to evaluate chemotherapy options associated with less toxicity. Nedaplatin (cis-diammine-glycoplatinum) is a derivative of cisplatin developed in Japan. Different small series have demonstrated that this agent appears to have similar efficacy with lower renal and gastrointestinal toxicities compared to cisplatin [40]. Performance of non-inferiority randomized trial with nedaplatin could help identify less toxic chemoradiation regimens.

Is There Benefit of Adding Chemotherapy to Extended Field Radiation for Patients with Known Para-Aortic Disease?

An additional area of controversy is the appropriate treatment of patients with para-aortic nodal metastases. The three previously discussed landmark randomized trials regarding chemoradiation for locally advanced disease specifically excluded these patients from their analysis. Three cooperative group trials have been published examining the effect of extended field radiation in addition to chemotherapy in women with positive para-aortic nodes. In 1998, the RTOG published the results of their phase II trial of 30 patients with clinical stage I through IV disease and positive para-aortic nodes who received twice daily extended field radiation in addition to intracavitary brachytherapy with two to three cycles of concomitant chemotherapy [41]. The chemotherapy regimen consisted of cisplatin (75 mg/m^2 given on days 1 and 22) and 5-FU (1,000 mg/m^2 daily on days 1 through 4 and days 22 through 25). The total external radiation doses were 24–48 Gy to the whole pelvis, 12–36 Gy parametrial boost, and 48 Gy to the para-aortics with an additional boost to a total dose of 54–58 Gy to the known metastatic para-aortic site. One or two intracavitary applications were performed to deliver a total minimum dose of 85 Gy to point A. The long-term follow-up to this trial was published in 2001, and the overall survival estimates were 46 % at 2 years and 29 % at 4 years. The probability of local-regional failure was 40 % at 1 year and 50 % at 2 and 3 years [42]. However, there were unacceptably high rates of acute and late grade 3 or 4 gastrointestinal toxicity (50 and 34 %, respectively). Unacceptably high rates of both acute and late toxicity were

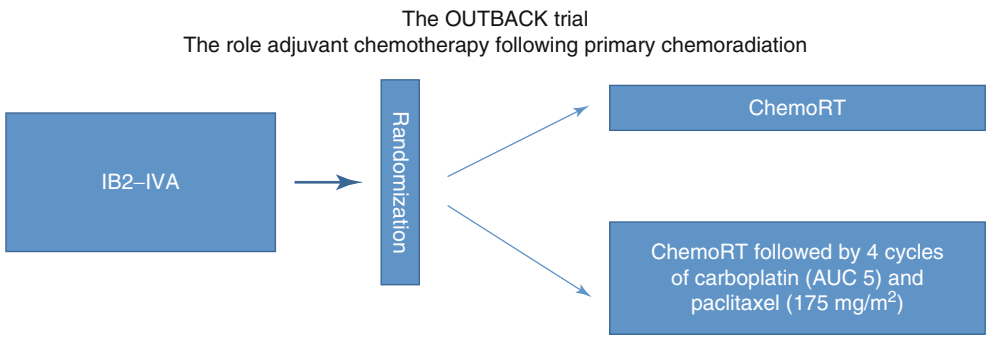

Fig. 8.5 Schema for the OUTBACK trial, a phase III, randomized controlled trial in patients with locally advanced disease treated with combined chemotherapy and radiation and then randomized to receive either adjuvant chemotherapy or no further treatment

also noted in a subsequent phase II, two-arm RTOG trial published in 2007 in which 26 women with para-aortic or high common iliac nodes were treated with extended field radiation delivered at a dose of 45 Gy with 1.8 Gy per fraction in addition to intracavitary radiation and concomitant weekly cisplatin (40 mg/m^2) [43]. Patients in the second treatment arm also received amifostine before each fraction of radiation in an effort to reduce toxicity. In a report of results from the arm with patients who were not treated with amifostine, rates of acute and late grade 3 or 4 gastrointestinal and hematologic toxicity were 81 and 40 %. In the second arm of the study, after a median 23-month follow-up, 87 % of patients experienced grade 3 or 4 acute toxicities and 20 % experienced grade 3 or 4 late toxicities [44]. Similar oncologic outcomes were noted in a GOG study of radiation delivered with standard fractionation and concomitant chemotherapy consisting of 5-FU (1,000 mg/m^2/day for 96 h) and (cisplatin 50 mg/m^2 in weeks 1 and 5) in 95 women with positive para-aortic nodes [45]. The 3-year overall and progression-free survival rates for the entire group were 39 and 34 %, respectively. Survival rates for those with stage I and II disease were 50 and 39 %, respectively. The dose to the para-aortic nodes was lower than the dose in the previously discussed RTOG study (45 Gy delivered daily at 1.5 Gy per fraction), resulting in lower rates of gastrointestinal toxicity. While increased rates of acute toxicity have been consistently demonstrated in regimens utilizing concomitant chemotherapy and radiation, the survival advantage shown in the majority of randomized trials argues in favor of this treatment modality in this high-risk subset.

Chemotherapy for Recurrent or Metastatic Cervical Cancer

Women with widely metastatic and/or recurrent cervical cancer represent a difficult group of patients to treat. This treatment dilemma often arises in the setting of recurrent disease, especially given the lower response rate in those patients previously treated with concurrent chemotherapy. It is unclear if treatment with chemotherapy offers any meaningful survival advantage when compared to supportive care. There are no randomized trials that have demonstrated overwhelming survival benefit for chemotherapy in this setting. Chemotherapy is most often given with a palliative intent in this situation. Fifty-eight cytotoxic agents have been tested in recurrent or advanced cervical cancer, and 21 of them have had clinical activity as defined by a response rate of 15 % or greater [46]. The most active single agents have been cisplatin, paclitaxel, topotecan, vinorelbine, and ifosfamide [47]. Multiple platinum-based regimens have been tested, and improved response rates have been demonstrated for the combinations of cisplatin and ifosfamide (31 %) and for cisplatin and paclitaxel (36 %) [48, 49]. The only trial that has shown a statistically significant improvement in survival for multi-agent chemotherapy over cisplatin alone was published by the GOG in 2005 [50]. This trial randomly assigned 356 women with stage IVB recurrent or persistent cervical cancer to treatment with three different chemotherapy protocols. The treatment arm consisting of methotrexate, vinblastine, doxorubicin, and cisplatin was closed early due to four treatment-related deaths in the 63 patients that had been treated. Compared to cisplatin alone (50 mg/m^2 given on day 1 every 3 weeks), the group treated with a combination of cisplatin and topotecan (0.75 mg/m^2 days 1–3 every 3 weeks) had a statistically significant improvement in response rate (27 vs 13 %), progression-free survival (4.6 vs 2.9 months), and median overall survival (9.4 vs 6.5 months). Rates of grade 3 and 4 hematologic and gastrointestinal toxicities were overwhelmingly higher in the group treated with cisplatin and topotecan.

In 2009, the GOG published the results of a phase III trial comparing four different cisplatin-containing doublets in stage IVB, recurrent or persistent cervical cancer. There were 513 enrolled patients who were randomized to therapy with cisplatin (50 mg/m^2 given on day 1 every 3 weeks) along with either paclitaxel (135 mg/m^2 given on day 1 every 3 weeks), vinorelbine (30 mg/m^2 given on day 1 and day 8), topotecan (0.75 mg/m^2 given on day 1, 2, and 3 every 3 weeks), or gemcitabine (1,000 mg/m^2 given on day 1 and 8 every 3 weeks). While there was a trend towards an improved RR, PFS, and OS for the cisplatin and paclitaxel doublet, there was no significant difference among the four arms. The toxicities in the four different arms were comparable, and the authors note that the different dosing schedules should be taken into account when deciding on the individual regimen [51]. The GOG has recently closed a phase III trial (GOG 240) of 452 advanced and recurrent cervical cancer patients randomized to treatment with paclitaxel and cisplatin, with and without bevacizumab, or topotecan and paclitaxel, with and without bevacizumab. Those patients who were treated with chemotherapy alone had a median overall survival of 13.3 months, and the patients who were treated with a combination of chemotherapy and bevacizumab had a median overall survival of 17 months, and this improvement was statistically significant. The Japanese GOG is currently enrolling a similar group of patients in a trial comparing cisplatin and paclitaxel to carboplatin and paclitaxel.

What Is the Evidence Supporting the Use of Targeted Therapy and Chemotherapy for Recurrent Cervical Cancer?

Numerous agents that target the vascular endothelial growth factor (VEGF) pathway are in clinical development, including agents targeting the VEGF ligand and agents targeting the

VEGF receptor. Among them, bevacizumab is the most promising drug in gynecologic cancer. A phase II trial from the GOG of bevacizumab in the treatment of 46 patients with persistent or recurrent cervical cancer was reported in 2009. Median PFS was 3.4 months and median OS was 7.3 months. These results compare favorably with historical controls. Bevacizumab seems to be well tolerated and active in second and third line treatment with recurrent cervical cancer [52]. RTOG 0417 was a phase II study of 49 patients treated with bevacizumab in combination with concurrent radiotherapy and cisplatin in stage IIB–IIIB disease or IB–IIA disease with biopsy-proven pelvic nodal metastasis and/or tumor size of at least 5 cm [53]. Bevacizumab was administered intravenously every 2 weeks during treatment at a dose of 10 mg/kg. The primary endpoint of the trial was toxicity, and per the preliminary results, reported in 2012, there were no serious adverse effects of treatment. Survival data has not yet matured.

The GOG reported a phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer in 2010. These agents are tyrosine kinase inhibitors that target the VEGF receptor, platelet-derived growth factor receptor, and epidermal growth factor receptor. In this randomized trial of 230 patients, pazopanib monotherapy demonstrated improved progression-free survival and a favorable toxicity profile [54].

Conclusions and Future Directions

In summary, while the use of chemotherapy in the management of cervical cancer has undergone a significant evolution over the past 15 years, many questions remain and are the subject of current randomized trials. International collaboration remains a focus for the completion of these trials. It is hoped that definitive results will answer questions regarding the efficacy of neoadjuvant and adjuvant chemotherapy, concurrent chemotherapy in intermediate-risk disease, and alternative dosing strategies for concurrent cisplatin and radiation. Current trials focus on pelvic-confined disease, and specific investigations of therapies directed at para-aortic positive patients are needed. Future directions should also include the continued exploration of the biology of cervical cancer with the hope of identifying targets for therapeutic agents.

Concluding Comments

- International collaboration to complete current randomized trials.
- Develop innovative trials for patients with para-aortic lymph node metastasis.
- Continue research to develop targeted agents.

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Response as a Measure of Treatment Efficacy in Clinical Trials: Should RECIST Be Abandoned?

9

Michael Friedlander and James Tate Thigpen

Summary Points

- Which is the optimal endpoint for clinical trials involving newly diagnosed ovarian carcinoma?
- What are the perceived shortcomings of the RECIST criteria for assessing response as an endpoint?
- When applied to clinical trials in ovarian carcinoma, are the RECIST criteria useful and reliable?
- Are there special circumstances (tumor markers, targeted therapy) in which the impact of therapy on the disease makes the application of RECIST criteria problematic?
- Should we abandon the RECIST criteria as a valid approach to evaluating response to therapy? If not, how should we incorporate new findings into the assessment of response?

Introduction

Progress in the field of cancer treatment depends on the demonstration of the efficacy and tolerability of approaches to patient management. The vehicle for the demonstration of treatment efficacy and tolerability is the clinical trial. Of the utmost importance to the success of a clinical trial in describing accurately the results of treatment is the clear definition of appropriate study endpoints. Current trials generally include three categories of endpoints: observational endpoints, patient-reported endpoints, and toxicity endpoints. The great majority of cancer clinical trials establish a primary observational endpoint as well as secondary endpoints that include options from all three categories. The primary endpoint is most commonly selected from three options: objective response, progression-free survival, and overall survival. The following discussion addresses briefly the relative merits of these three endpoints and then focuses on the role of objective response in current and future cancer clinical trials, in particular trials in gynecologic cancers.

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The Endpoint Controversy

The Fourth Ovarian Cancer Consensus Conference (OCCC) of the Gynecologic Cancer Intergroup (GCIG) concluded unanimously that an appropriate endpoint for a cancer clinical trial should reflect clinical benefit [1]. For those trials that focus on treatment efficacy, three endpoints constitute the focus of most studies: response rate (complete response rate also considered), progression-free survival (time to progression is occasionally also assessed or substituted), and overall survival. Of these three, only overall survival is accepted as independently reflecting clinical benefit and therefore is regarded as the gold standard endpoint. In fact, three reasons are generally cited as to why overall survival should be regarded as the gold standard endpoint: (1) as noted already, extension of life is widely accepted as reflecting benefit for the patient; (2) death is definitive and the time easily determined; and (3) historically, therapies that are truly active generally prolong survival.

There are, however, several caveats that must be considered. First, there is no clear definition of what constitutes "clinical benefit." Those who contend that overall survival is the endpoint that reflects clinical benefit define prolongation of survival as a clinical benefit. It is thus a self-fulfilling prophecy that overall survival reflects clinical benefit despite the obvious fact that one can easily envision circumstances in which prolonged survival is not a clinical benefit (e.g., spending the last 3 years of life on a ventilator). Criticism of progression-free survival and response rate as endpoints contends

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that neither has been shown to reflect clinical benefit since neither has been shown to reflect improved survival. The truth is that one cannot make a statement as to whether any endpoint reflects clinical benefit until one develops a reasonable definition of "clinical benefit." If clinical benefit means simply prolongation of survival, then overall survival is the only endpoint associated independently with clinical benefit. If, on the other hand, the definition of clinical benefit includes other parameters such as reduction in the volume of disease (response), prolongation of time until progression takes place (progression-free survival), or reduction of disease-related or treatment-related symptoms (health-related quality of life), then these become appropriate measures of clinical benefit. The Ovarian Cancer Consensus Conference [1] concluded that, in addition to overall survival, response and progression-free survival reflect clinical benefit because these measure parameters that are important to patients and that reflect improvement in the patient's circumstances, but the conference did not offer a clear definition of "clinical benefit."

Secondly, there are evolving arguments as to why, in certain cancers such as ovarian cancer, progression-free survival in particular might better reflect the efficacy of the study treatment than overall survival. Once an ovarian cancer patient on a phase III trial progresses on a particular treatment, she goes "off study" and can receive additional treatment. Contrary to the situation for ovarian cancer prior to the introduction of taxanes, there are now at least 21 additional active agents to which the patient has not been exposed that are available for further treatment [2–22]. Particularly in those patients who achieved a complete response to prior therapy, the additional treatment has the capacity to alter survival significantly [23]. Since there is no way to control the type of therapy each patient receives, this additional therapy can potentially alter survival and thus confound any advantage the study therapy might offer. This is particularly true when the experimental therapy is commercially available, and the patients assigned to the control regimen can cross over to the experimental treatment [24, 25]. Under such circumstances, progression-free survival may provide the best assessment of the relative merits of regimens compared in a phase III trial, and overall survival may reflect a chance observation among a myriad of variables of types of therapy received.

Third, certain of the newer targeted agents increase the number of patients who exhibit stable disease without an increase in response rate. This prolongs progression-free survival without an increase in response rate and often without an improvement in overall survival [26–29]. Progression-free survival would seem to reflect better the impact of such treatment on the disease.

There are thus reasonable arguments to support the use of both overall survival and progression-free survival as primary endpoints particularly of phase III cancer clinical trials.

Response by RECIST as an Endpoint

Where does this leave measurement of response as an endpoint? The answer to this question will unfold as follows:

1. The evolution of current response criteria (RECIST)
2. Critique of response assessment by RECIST in ovarian cancer
   (a) RECIST criteria (complexity, arbitrariness)
   (b) Application of RECIST (usefulness, reliability)
   (c) Special circumstances (tumor markers, targeted therapy)
   (d) Clinical benefit
3. Conclusions

Evolution of Current Response Criteria

The RECIST (Response Evaluation Criteria in Solid Tumors) International Working Group developed criteria for tumor response in 2000 (RECIST 1.0) in an effort to standardize the measurement of the change in tumor size in patients receiving chemotherapy in phase 2 clinical trials [30]. This was an extension of the World Health Organization (WHO) tumor response [31] criteria that had been introduced in 1981. Modification was believed to be necessary because of a number of perceived shortcomings and the associated measurement errors. As examples of these shortcomings, neither the required bidimensional method of measurement nor the criteria for the selection of target lesions were clearly described in the WHO guidelines. Tumor response was often found to be poorly reproducible with inter- and intraobserver variability [32]. In addition, a number of modifications of the WHO criteria by individual groups resulted in response criteria being no longer comparable between different investigators and trial groups. Because of these problems, the working group developed RECIST 1.0 [30].

Among a number of important differences between WHO and RECIST 1.0, possibly the biggest change, was the substitution of unidimensional measurements of lesions for the bidimensional measurements in the WHO criteria. The definition of complete response was essentially the same, but the definition of partial response in RECIST required at least a 30 % decrease in the sum of longest dimensions (LD) from baseline and confirmation at 4 weeks. The RECIST working group provided definitions for measureable and nonmeasurable disease that are quite complex and are also prone to reading error. Nonmeasurable lesions included small lesions with a longest diameter of <10 mm and, particularly relevant to ovarian cancer, also include ascites, pleural effusions, and cystic or necrotic lesions. Target lesions were to be selected on the basis of their size and suitability for accurate repeated measurements. They recommended that up to five target lesions per organ and 10 in total should be measured at

baseline. Nontarget lesions included all other lesions or sites of disease. Measurements of nontarget lesions were not required, but the presence or absence of each nontarget lesion needed be noted at baseline and on follow-up scans. They also provided definitions for complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) which had some differences from the WHO criteria. The CR and PR definitions are described above. PD was defined as at least a 20 % increase in the sum of the longest diameters or the appearance of new lesions.

The attempt to standardize the criteria for measuring response was admirable, and the new criteria were widely adopted by trials groups and the pharmaceutical industry and were supported by regulatory agencies. In a comparison of response using either WHO or RECIST in a number of solid tumors, but notably not ovarian cancer, the WHO and RECIST criteria were reported to be equivalent in terms of response rates [33–36]. It was furthermore reported that the unidimensional measurement correlated well with the three-dimensional volume measurement by helical CT [37]. Despite this, many radiologists found RECIST too cumbersome to be used in daily practice, and concerns were raised by clinicians as well [38–40]. In addition a number of other investigators argued that current drug development and the testing of molecularly targeted agents required different outcome measures and better endpoints than RECIST [41, 42].

The guidelines were later modified in 2009 (RECIST 1.1) [43]. The number of target lesions to be assessed was reduced from five per organ to two per organ in an attempt to simplify the criteria, which are complex. RECIST 1.1 provided detailed instructions about how to measure and assess lymph nodes as these were not included in RECIST 1.0. CR by RECIST 1.1 requires the disappearance of all target lesions and a reduction in the short-axis measurement of all pathologic lymph nodes (whether target or nontarget) to <10 mm. PD for target lesions according to RECIST 1.1 requires a 5-mm absolute increase of the sum of the longest diameters of the target lesions in addition to a 20 % increase in the sum of the target lesions. When measurable disease or a target lesion is present, progression of disease can be declared as a result of an overall substantial worsening in nontarget disease leading to an overall increase in disease burden even with SD or PR in target disease. One of the other major changes in RECIST 1.1 was the inclusion of FDG PET in the detection of new lesions that define progression, but it was felt that it was too soon to include functional imaging to measure response.

Critique of Response Assessment by RECIST in Ovarian Cancer

The criticism of response assessment by RECIST falls into four categories: alleged problems with the RECIST criteria themselves, application questions about the usefulness and reliability of RECIST, potential problems in specific circumstances, and the issue of whether RECIST-based response correlates with clinical benefit.

RECIST Criteria: Complexity

The attempt to standardize the criteria for measuring response was admirable, and the new criteria were widely adopted by trials groups as well as the pharmaceutical industry and regulatory agencies. Despite this, many radiologists found RECIST too cumbersome to be used in daily practice, and clinicians raised concerns as well [38–40]. These concerns are compounded by the fact that guidelines do not require that the same individual measure lesions at each prospectively designated assessment point. Under such circumstances, the more complex the criteria are, the more likely errors creep into the assessment.

Before one assumes that issues related to complexity devalue the RECIST response endpoint, however, one must remember why the RECIST criteria are as complex as they are. One of the major criticisms of the WHO criteria for response was that the criteria for measurement and for target lesion selection were not clearly spelled out. The RECIST criteria clearly define target lesion selection, simplify lesion measurement by limiting the measurement to one dimension, and define these criteria for different types of target lesions. The revision in 2009 (RECIST 1.1) reduces the number of required target lesions and improves the criteria for assessment of lymph nodes. All of these steps answer major criticisms of the WHO criteria and RECIST 1.0 and, in the case of the 2009 revision, reduce the complexity to some extent. More importantly, the working group for the development of RECIST 1.1 did not yield to the temptation to require that the same investigator do all measurements which, even though ideal, would have been virtually impossible to carry out consistently.

In summary with regard to complexity, one has to concede that the RECIST criteria are complex and can be cumbersome to carry out. Opinions as to whether RECIST 1.1 addressed these concerns sufficiently vary. On the positive side, however, the criteria are sufficiently detailed that consistency in application probably is better than was the case with the WHO criteria. Although complexity remains a concern, it is probably not a fatal flaw for response assessment.

RECIST Criteria: Arbitrariness

A second major criticism of the RECIST criteria is that they exhibit a significant degree of arbitrariness in characterizing each patient as having a positive or negative result and in selecting points that separate a positive from a negative observation. Michaelis and Rattain in a critical commentary on RECIST make the point that "although RECIST does address some of the apparent deficiencies in the WHO

criteria they do not overhaul the underlying assumptions and still categorize individuals as responders and non-responders as opposed to measure the amount of response" [41]. Response is determined by a cutoff of a 30 % decrease in the sum of the largest diameters of target lesions, but the rationale for the choice of the 30 % decrease is not clear [30]. A similar statement can be made about the 20 % increase required to define progression. It is pertinent that the lead author of the RECIST 1.1 guidelines recognizes the limitations of the RECIST definitions and has recently written that "it seems unlikely that there would be a substantial difference in an individual patient state if he/she experiences a 19 % versus 21 % increase in disease or a 29 % versus 31 % decrease in disease. However, in the first instance these changes signal the difference between stable and progressive disease and the second, the difference between stable disease and partial response" [44]. This demonstrates the arbitrariness of definitions that were intended to aid in identifying active agents in phase 2 trials and no more.

As an alternative to RECIST in the assessment of response in phase II trials of new agents, waterfall plots have been used to chart each individual patient's response and provide a measure of the "amount of response" [45]. In contrast to averaging of patient responses and reporting response rates, waterfall plots clearly demonstrate the variability of "tumor response" independent of arbitrary tumor response criteria. Arguably, this is a more informative and less arbitrary way to measure treatment effect in phase 2 trials where response is the primary endpoint. Waterfall plots can be used to demonstrate the change in tumor size as well as the change in CA125 and provide more information than RECIST response or GCIG CA125 response alone.

One major caveat to the criticism that RECIST is arbitrary in its definitions and applications must be considered. In every study, certain criteria are arbitrarily applied to each study endpoint to define what would constitute a positive or a negative study. For example, in establishing overall survival or progression-free survival as trial endpoints, a certain level of difference between the study regimens is defined as being significant and therefore a positive result. The selection of that point can be described as arbitrary. In defining what is meant by progression, arbitrary definitions are set so that the patient outcomes can be assessed to determine whether progression-free survival is different between the treatment regimens being compared. Criteria to assess even a waterfall plot to determine whether a result is positive or negative must be set. Criticizing RECIST as arbitrary sets a bar that would invalidate any endpoint. What is critical to clinical trial design is prospectively establishing for each endpoint what would constitute a positive or a negative result. Without this, the study would not be interpretable.

In summary with regard to arbitrariness, it is true that the RECIST criteria are to some extent arbitrary in the definitions of what constitutes a response. This is necessary in order to define what would constitute a positive study.

RECIST Application to Trials: Usefulness

It is now increasingly accepted that "ovarian cancer" is not one disease and comprises a number of histological subtypes which all have very different and distinct biological behavior, natural history, and response to treatment [46, 47]. For example, clear cell ovarian cancers have more in common with clear cell cancers of the kidney than they do with serous ovarian cancers [18]. Furthermore, serous cancers, which are the most common histological subtype, are divided in low-grade, type 1 serous cancers, or high-grade, type 2 serous cancers, and they are very different with respect to molecular pathogenesis and behavior [48]. Low-grade or type 1 ovarian cancers are characterized by BRAF and KRAS mutations [48]. They have very low objective response rates to chemotherapy, but there is increasing interest in treating these tumors with molecularly targeted agents where stable disease rather than objective response is the primary endpoint and where functional imaging could be far more useful than objective response by RECIST to assess therapeutic benefit. In contrast, the fimbria of the fallopian tube appears to be the site of origin of many, if not most, high-grade or type 2 serous cancers which are commonly labeled as ovarian or peritoneal cancers [48]. To add to the complexity, there are at least five different molecular subtypes of high-grade serous cancers which differ with respect to pattern of spread, prognosis, and response to treatment [46]. It is simplistic to believe that a simple metric such as RECIST to measure objective response is applicable to all of these different tumors which have all been "lumped" together as "ovarian cancer" in the past. Furthermore, in contrast to many other solid epithelial cancers, aggressive surgical debulking is standard of care, and since most patients with newly diagnosed "ovarian cancer" will not have measurable disease after surgical debulking, the endpoint of treatment is progression-free survival or overall survival. Secondary debulking is also now being practiced widely, and many patients who have late relapses will be operated on in an attempt to reduce tumor volume. Most of these patients will not have measurable disease. Even in patients who do not have secondary debulking, recurrent ovarian cancers can be notoriously difficult to "measure" on a CT scan, and it has been estimated that over 50 % of patients with recurrent disease do not have measureable disease using RECIST [49]. Finally, the primary aim of treatment in patients with platinum-resistant recurrent ovarian cancer is palliation and symptom control, and this cannot be measured using objective response rates which are uniformly low and less than 10 % in most phase 3 trials. Measuring symptom benefit is far more important than RECIST response in this setting [50].

In contrast to all of the above which suggests that RECIST response is of little or no value in clinical trials of ovarian cancer, response can be a very important endpoint if used correctly. First, the heterogeneity of what we have traditionally called ovarian cancer is not a reason to abandon RECIST response as an endpoint. This observation is instead a reason to use our newly acquired biologic understanding of the disease to focus our trials on the appropriate patients and to choose the appropriate endpoints for the particular trial. The Gynecologic Cancer Inter Group (GCIG) is currently studying low-grade serous carcinomas in separate trials from the high-grade serous and endometrioid carcinomas and conducting separate trials in mucinous and clear cell carcinomas. Different therapeutic approaches are being tested for each of these subtypes of ovarian carcinoma. In those studies of agents that can reasonably be expected to induce objective responses if active, RECIST response rate would be a perfectly appropriate endpoint.

Secondly, the lack of measurable disease in patients who have tumors that have been successfully debulked does rule out the use of RECIST response as an endpoint for other situations in ovarian cancer. In the population with platinum-resistant recurrent disease, a substantial number of patients will have measurable disease, and the use of response rate as an endpoint has been accepted by even regulatory agencies such as the FDA for accelerated approval of new agents. The most recent example of approval by response rate came in 1999 with the accelerated approval of liposomal doxorubicin by the FDA in patients with platinum/paclitaxel refractory ovarian carcinoma (see FDA website for press release and announcement). To the contrary, however, the FDA has never approved an agent in ovarian cancer based solely on symptom benefit.

In summary regarding usefulness of RECIST, it is true that there are situations in which RECIST response is not an appropriate endpoint: populations with no measurable disease and populations best treated with targeted or other agents that do not induce objective responses. RECIST response, on the other hand, is a very appropriate endpoint in studies evaluating regimens that induce objective responses, particularly in studies of platinum-resistant disease evaluating new agents in phase II trials to determine whether the agent is active.

RECIST Application to Trials: Reliability

The general assumption on which RECIST is based is that unidimensional tumor measurements can be reliably performed by different readers and are accurate and reproducible. Given that response rates are often used as the primary endpoint in phase II clinical trials and can affect the outcome of these studies, reliability is of utmost importance. The decision whether to take the investigational agent into larger and more definitive phase III studies is often based on the response rates in phase II studies; hence, clearly a lot is at stake. There have not been any studies into the interobserver and intraobserver variability in tumor measurement in ovarian cancer, although there have been studies in other tumor types which have all raised concerns about the reliability of RECIST reporting [51, 52]. Measuring lung metastases is easier than measuring peritoneal nodules or omental "thickening" which are common in ovarian cancer, but even with these more "easily measurable" lesions, measurement of lung tumor size on CT is often inconsistent and leads to incorrect interpretation of tumor response [51]. This is particularly evident if the tumor is irregular in size. In one study, progressive disease was erroneously determined to have occurred in 43 % of lung tumors that were measured by different observers and in 21 % of cases when measured by one observer. RECIST guidelines do not stipulate that the same observer perform all serial measurements, and it is very likely that multiple readers of varying expertise will perform tumor measurements in patients entered on clinical trials. It is very possible that variations between readers could either overestimate or underestimate the activity of the investigational agent and lead to a potentially active agent being discarded or an inactive agent being taken to phase III. Even independent radiological review is not immune from variability in assigning response on the basis of RECIST that is often reader dependent and not a guarantee of perfection [52]. It is possible that emerging software tools could reduce the systematic and random errors of RECIST reporting, but these are costly, require sophisticated analyses, and are not widely available [40].

Once again, the charge that RECIST response is not sufficiently reliable to be a valid endpoint in clinical trials of ovarian cancer is a broad general contention to which caveats must be applied. First, as was noted above, there are no studies looking at the reliability of RECIST response in ovarian cancer. The fact that variability of measurements between different readers has been shown in lung cancer does not necessarily apply to ovarian cancer. In lung cancer, calcification of lesions and use of different windows in reading the CT scan can result in variability in interpretation; neither of these factors play a role in ovarian cancer [53]. Secondly, there are registration trials using independent review which show concordance between investigator review and independent review of scans by RECIST criteria [54, 55]. While independent review is not perfectly concordant, more often than not this shows that RECIST can be applied in a consistent and reliable fashion. Thirdly, the issue of 10-mm cuts creating problems in assessing tumor measurements is a problem that is fading as technology improves. Scanners with 5-mm and even 1.25-mm cuts are increasingly common and should solve these issues. Fourthly, in a comparison of response using either WHO or RECIST in a number of solid tumors not including ovarian cancer, the WHO

and RECIST criteria produced equivalent response rates [33–36]. It was furthermore reported that the unidimensional measurements correlated well with the three-dimensional volume measurements by helical CT [37]. The WHO criteria were used for at least two decades in assessing response and in approving agents for use. RECIST response is at least as reliable as the WHO criteria and offers the advantage of much clearer definitions of criteria and methodology.

In summary regarding reliability, there are some legitimate concerns about the reliability of RECIST assessment of response. These concerns, however, have never been demonstrated in ovarian cancer per se but rather are extrapolated from other tumor types and may or may not apply. The principal lessons to be drawn are that assessment of response should be independently reviewed where feasible and should be conducted in a way that accounts for recognized potential problems. Issues of reliability do not constitute valid reasons for abandoning RECIST response as an endpoint.

Special Circumstances: CA-125

The member groups of the GCIG have reached consensus regarding the criteria that should be used to define progression-free survival after first-line therapy as well as the criteria to define response to treatment in recurrent ovarian cancer using serum CA-125 [56]. The GCIG has specified how these criteria should be used. A CA-125 response is defined as at least a 50 % reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated provided they have a pretreatment CA-125 that is at least twice the upper limit of normal and within 2 weeks of starting the treatment. The date when the CA-125 level is first reduced by 50 % is the date of the CA-125 response. CA-125 is of benefit to assess response in patients who do not have measureable disease, and this may be up to 50 % of patients with recurrent ovarian cancer. Progressive disease is conventionally defined by RECIST 1.1 but can also be based on CA-125 progression after first-line therapy that is defined as a doubling of the CA-125 level from the nadir value on 2 occasions at least 1 week apart.

There are many advantages to using CA-125 over RECIST [56]. CA-125 levels are more objective and much less likely to be associated with measurement error. It is much cheaper than radiological investigations and widely used in clinical practice. The majority of patients with recurrent ovarian cancer have an elevated CA-125 in contrast to the much small number of patients that have measurable disease by RECIST. The concordance between image-based tumor response and response by CA-125 criteria is quite variable, with the frequency of CA-125 responses generally higher than that of RECIST responses [57]. Arguably the discordance is most likely to be due to the problems with RECIST response which have been detailed previously rather than to the overcalling of response by CA-125. Furthermore, there are data to show that response assessment by GCIG CA-125 criteria is superior to RECIST in predicting survival in patients receiving second-line chemotherapy for recurrent ovarian cancer [58]. Interestingly, in this study, in contrast to CA-125 response, RECIST response had no demonstrable independent influence on survival in patients with recurrent ovarian cancer receiving second-line therapy [58]. Waterfall plots have also been used to trace the fall in CA-125 levels in clinical trials and are possibly also a better way to assess "activity" of an investigational agent rather than using arbitrary cutoff levels. CA-125 has many advantages over RECIST1.1, but the regulatory agencies remain fixated on RECIST, and this strongly influences the design of registration trials by pharmaceutical companies.

On the other hand, contrary to the argument above that CA-125 response should replace RECIST response, both are reasonable endpoints in ovarian cancer trials. There are no data that show that only those endpoints that are effectively surrogates for overall survival should be considered valid endpoints. The argument that, because one study shows no correlation between RECIST response and survival, RECIST response should be abandoned is therefore without basis. The literature as a whole supports both endpoints as valid ways to assess treatment efficacy. There are, however, two real problems with CA-125 as an endpoint. The first real problem with response based on CA-125 as an endpoint, however, is clearly stated above: regulatory agencies remain fixated on RECIST. The US FDA does not accept CA-125 as a measure of response or progression in ovarian cancer. Since new agents must be approved before they can be used outside of clinical trials, registration trials must be based on endpoints other than CA-125 response. The second real reason is that some agents can alter the CA-125 independently of actual tumor response. Among cytotoxic agents, pegylated liposomal doxorubicin (PLD) is a prominent example [59]. Up to 25 % of ovarian cancer patients who respond to PLD by RECIST and CA-125 criteria will show an initial rise in CA-125 after one cycle of therapy. In addition, there are concerns that some of the newer targeted agents can alter CA-125 levels independently of tumor response.

In summary regarding CA-125 response, criteria developed by the GCIG provide a clear basis for using CA-125 response as a trial endpoint. Two caveats prevent this endpoint from enjoying widespread use. First, regulatory agencies do not recognize CA-125 response as a valid regulatory endpoint. Secondly, some agents, particularly some of the newer targeted agents, may interfere with CA-125 levels and thus obfuscate appropriate interpretation of this endpoint.

Special Circumstances: Targeted Agents

RECIST does not take into account that a change in tumor size may not always be due to disease response or progression [40].

In the new era in cancer treatment that is dawning, it seems very likely that many patients with ovarian cancer will be treated with targeted therapies which are quite different from cytotoxic chemotherapy. This raises questions regarding the value of using RECIST to measure benefit [40–42]. It is well recognized that targeted therapies including angiogenesis inhibitors such as bevacizumab or tyrosine kinase inhibitors may cause a paradoxical increase of tumor size despite response because of hemorrhage, necrosis, or fluid shifts. This has been reported to occur in a number of tumor types such as renal cancer, hepatocellular carcinoma, GIST, melanoma, and high-grade gliomas. Indeed, there are now specific criteria used to evaluate response to drugs such as imatinib in GIST due to the shortcomings of RECIST; the overall tumor CT attenuation decreases dramatically with response and can produce myxoid degeneration, hemorrhage, necrosis, and a paradoxical increase in tumor size [60]. Similar criteria have been developed for evaluating response in renal tumors to tyrosine kinase inhibitors such as sunitinib which can induce extensive necrosis in metastatic renal cell cancer [61]. For example, van der Veldt et al. recently reported that the Choi criteria had a significantly better predictive value for progression-free survival and overall survival than RECIST in renal cancers and that the Choi criteria could be helpful to define early which patients who were most likely to benefit from sunitinib [61]. As mentioned earlier, clear cell ovarian cancers have much in common with renal cancers, and there are studies in progress to evaluate the role of tyrosine kinase inhibitors in clear cell ovarian cancers [47]. Based on the results from renal cancers, it would be worthwhile including Choi criteria to assess response in these studies as well.

It is likely that we will need to develop functional response criteria to determine the activity of targeted therapies in ovarian cancer and that RECIST will be of limited value when cytostatic agents are being evaluated in clinical trials. It is conceivable that a targeted agent could be very active in delaying time to tumor progression without meeting criteria for RECIST response or even meeting criteria for progression due to paradoxical increase in tumor volume as discussed above. A good example of the limitations of RECIST is evident from a randomized placebo-controlled trial of sorafenib in metastatic renal cancer. The objective RECIST response rate was 4 %, but the median progression-free survival was 23 weeks versus 6 weeks in the two arms. These effects were confirmed in a randomized phase III trial [62, 63].

While the special circumstance of the use of targeted agents does pose difficulties for RECIST response as an endpoint, it is an overstatement that RECIST response should be abandoned. If a particular agent clearly does not produce objective responses as defined by RECIST or, worse, produces effects that may be confused with progression, then clearly RECIST response would not be appropriate as an endpoint. Several contentions by those in favor of abandoning RECIST response, however, clearly are speculative. There are no substantial data on the use of functional response criteria for studies evaluating the targeted agents in ovarian cancer nor are there any data supporting the extrapolation of the Choi criteria to trials in ovarian cancer. As of now, use of the progression-free survival endpoint or a modification thereof (% progression-free at a fixed time point) would appear to be an appropriate endpoint for some of these trials. Rather than speculating about endpoints that have not been validated as a reason for abandoning validated endpoints, we should take a more thoughtful approach to study design and also account for such factors as the requirements of regulatory agencies in the case of registration trials. With this approach, RECIST response will still be of value in selected trials even of newer targeted agents.

Clinical Benefit

Ultimately the goal of therapy is to produce clinical benefit. The question as to what constitutes clinical benefit has become a difficult question. Many, including regulatory agencies such as the US FDA, have tended to regard only prolongation of survival as reflecting clinical benefit. The GCIG, at its most recent Fourth Ovarian Cancer Consensus Conference, attempted to define what an appropriate endpoint was and what constituted clinical benefit [1]:

> What are the appropriate endpoints for clinical trials in ovarian cancer? Appropriate endpoints for clinical trials should reflect the achievement of clinical benefit that is defined as improvement of one or more of the following subjective and objective endpoints: toxicity, time without symptoms, patient reported outcomes (PRO), progression-free survival (PFS), and overall survival (OS).

Objective responses are associated with improved symptoms related to the cancer [64]; hence, RECIST responses do correlate with at least one of the above criteria. On this basis, the use of response rate as a criterion for accelerated approval by the US FDA seems reasonable. In addition, in those instances where the agent under evaluation can reasonably be expected to produce objective responses, RECIST response remains a valid endpoint for ovarian cancer clinical trials.

Conclusions

The thesis of this discussion has been that we should abandon RECIST response as an endpoint for clinical trials in ovarian cancer. Based on all of the considerations presented, the answer is clearly that we should not abandon RECIST response as an endpoint in appropriate circumstances. This answer comes with a number of caveats that point us in a clear and appropriate future direction.

Why should we not abandon RECIST? Clinical trials have historically been grounded in "response rates," and this has been useful despite the shortcomings of all the definitions that have been used over the last 40 years. RECIST responses remain appropriate for assessment of activity of new agents that can be reasonably tested in patients with platinum-resistant measurable disease and can be expected to produce objective regression of disease. Even regulatory agencies recognize RECIST response rates in this setting as a basis for accelerated approval of new agents.

On the other hand, should we be actively using our expanding biological knowledge regarding ovarian cancer to develop new and better endpoints? The answer to this question is clearly yes. We need now to think beyond RECIST 1.1 not to replace RECIST 1.1 now but rather to progress in our ability to assess treatment efficacy in the future. It is clear that we need to develop response criteria that reflect not only the type of cancer being treated but also the mode of action of targeted therapies that are in many respects worlds apart from conventional cytotoxic agents. Many of these targeted agents have very low response rates according to RECIST but nevertheless can delay the time to progression that is probably a more important endpoint for individual patients than an arbitrary reduction is size of a tumor. These agents can also cause a paradoxical increase in tumor size secondary to necrosis or intratumoral hemorrhage or myxoid degeneration. Unless this is recognized, patients may be taken off an active treatment.

Endpoints also depend on the characteristics of the specific patient groups included in the trial. In an era of expensive targeted therapies and personalized care based on the molecular characteristics of the tumor, we need to develop robust and reliable functional assays to measure "response" early. There are many emerging functional imaging techniques including PET/CT, diffusion-weighted MRI, dynamic contrast-enhanced MRI, magnetic resonance spectroscopy, and radioimmuno-scintigraphy [42]. In particular, novel PET radiotracers that address specific metabolic pathways may provide a better assessment of therapeutic benefit of targeted agents than conventional imaging and RECIST1.1 [65]. It goes without saying that all these new modalities need to be assessed rigorously to ensure reproducibility and validity before they can actually be substituted for RECIST and are adopted into routine clinical practice.

Concluding Comments

- Among the three major categories of endpoints, progression-free survival may be the preferred because it is least impacted by confounding factors and, according to the GCIG Fourth Ovarian Cancer Consensus Conference, reflects clinical benefit.
- Response as assessed by the RECIST criteria remains a useful endpoint, is accepted by most regulatory agencies for approval of new agents and approaches, and should not be abandoned at the current time.
- Efforts to develop sufficient understanding of ovarian cancer biology to permit the incorporation of this knowledge into a new approach to assessing response should continue with the goal of replacing RECIST in the future with a more biologically based set of criteria.

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What Are the Treatment Options for Recurrent Ovarian Cancer?

10

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Summary Points

- Opportunities to use several lines of therapy for recurrent ovarian cancer have extended patient survival but present the treating physician with several clinical and sometimes challenging choices.
- Categorization of "platinum sensitivity" to choose therapies for recurrent disease is an empirical definition but still strongly influences decision-making.
- The role of surgery in recurrent disease and integration of molecular targeted therapies into the treatment pathway are the key research questions currently being addressed.

Introduction

The majority of patients with advanced ovarian cancer relapse or progress after primary therapy. The clinical management of these patients is complex as physicians and patients are often faced with many choices for further therapy, and in many cases, patients will receive a sequence of treatments to prolong their life. Evolving drug resistance eventually leads to a failure of treatment. Decisions about anticancer therapies need to balance the likely gain in life years with the quality of life of patients, including the amount of time they receive treatment. While there is little evidence that the cure rate of advanced ovarian has increased, survival has lengthened significantly over the last decade, and this is most likely due to the use of an increasing number of active drugs. In this chapter we discuss the choices available for treating patients with recurrent disease, including the option of surgery.

Does Surgery Have a Role for the Treatment of Recurrent Ovarian Cancer?

The use of cytoreductive surgery for patients with relapse within 6 months has not shown a meaningful benefit and is not therefore recommended. Retrospective data in patients with late relapse indicate that complete resection of recurrent tumor should be aimed for, since survival prolongation is mainly seen for patients with no residual disease [1]. The aim of surgery for recurrent ovarian cancer was also a topic at the 4th Ovarian Cancer Consensus Conference, Vancouver 2010, and it was stated that surgery for recurrent ovarian cancer might be beneficial for selected patients and the aim should be complete resection [2]. However, some series reported a survival benefit in patients with residual disease of 1 cm or more [3, 4]. However, these findings were not significant or had other limitations, such as case mix including early relapse, surgery for palliative care, or remarkably low survival rates in patients with 1 cm and more residual disease. In addition, a recent meta-analysis of most studies for surgery in recurrent ovarian cancer has found that obtaining complete resection in an additional 10 % of patients increases median survival by 3.0 months [5], even after controlling for all other studied variables.

Almost all series reported a relationship between survival and surgical outcome in univariate analysis. Complete debulking was one of the strongest predictors for survival in

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all multivariate analyses performed. All other analyzed factors provided controversial results. Treatment-free interval before cytoreductive surgery showed no significant impact on outcome in univariate analyses in about half of the series, but others reported a significant role. However, only few patients with rather short treatment-free interval were included in the respective series and the proportion of patients with less than 6 months ranged from 0 to 13.5 %. Therefore, the data about a possible impact of treatment-free interval are mainly valid for different periods beyond 6 months [6]. Eisenkop et al. reported a benefit for treatment-free intervals exceeding 36 months compared to shorter intervals (>36 months vs.13–36 vs. 6–12 months) [7]. The same applies to the series of Chi et al. (>30 months vs. 12–30 months vs. 6–12 months) [8]. Scarabelli et al. showed a benefit for the subgroup with a recurrence-free interval of 13–24 months but not for patients with longer (>24 months) or shorter intervals (7–12 months) [9]. The DESKTOP I trial showed a benefit for a treatment-free interval exceeding 6 months but no difference if intervals longer than 6 months were compared in the univariate analysis (6–12 vs. 12–24 vs. longer than 24 months) [1]. However, treatment-free interval did not remain an independent factor in the multivariate analysis. A similar observation was reported by Zang et al. who reported a benefit for longer progression-free intervals in univariate analysis which could not be confirmed by multivariate analysis [10].

But the question of how we could select candidates for secondary cytoreductive surgery in recurrent ovarian cancer still remains important. The DESKTOP I trial conducted by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) identified a combination of predictive parameters for complete resection: good performance status (ECOG 0), no residual disease after surgery for primary ovarian cancer (alternatively, if unknown: early initial FIGO stage), and absence of ascites in presurgical diagnostics. This score ("AGO score") for complete resection was validated in a prospective trial and showed that patients with good general condition (ECOG 0), no residual disease after surgery for primary ovarian cancer, and absence of ascites in presurgical diagnostics had a 76 % chance of undergoing complete resection [11]. Furthermore, it has already been shown that preoperative factors like peritoneal carcinomatosis are a negative predictor for complete resection [12].

Depending on the surgical expertise, postoperative morbidity and mortality rates vary, but complication rates in surgery for recurrent ovarian cancer are not significantly higher, compared to primary debulking surgery.

The morbidity rate in a meta-analysis of surgery in recurrent ovarian cancer ranged between 0 and 88.8 % with a weighted mean of 19.2 % [5]. In the DESKTOP II trial, 33 % of patients had at least one complication in the postoperative period, and the perioperative mortality was 0.8 %. Nevertheless, these data are likely to be affected by selection and publication bias, since there is no strict definition of morbidity for the observed time after surgery.

A recent Cochrane analysis regarding the value of cytoreductive surgery in addition to chemotherapy in patients with recurrent ovarian cancer could not identify eligible studies to answer this question [13]. Two prospective randomized trials evaluating the role of cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer are ongoing (AGO DESKTOP III, GOG 213).

What Are the Choices of Chemotherapy to Treat Recurrent Disease?

Should the Concept of Platinum Resistance Be Redefined?

Decisions on the type of treatment to use at relapse are still based on work conducted about 25 years ago when there were few options to choose. The concept of "platinum-sensitive" relapse arose from a series of reports in which patients relapsing at varying times after first-line platinum therapy were re-treated with cisplatin [14, 15]. On this basis patients were grouped into those with "platinum-sensitive" relapse, with disease recurrence more than 6 months after previous platinum therapy, and "platinum-resistant" relapse, occurring earlier than this. This has resulted in the construction of treatment algorithms with recommendations for treatment with drugs and drug combination that will be discussed below (Fig. 10.1). Modifications have been made to include "partially platinum-sensitive" relapse (6–12 months interval) and fully sensitive relapse (>12 months platinum-free interval) [16]. Similarly, there is a group that has been defined as platinum refractory, with disease progression while receiving platinum-based chemotherapy.

These categories arose from empirical observations and are not mechanistic. While there are now several other non-platinum drugs to choose, platinum drugs are probably still the most active agents at each phase of a patient's treatment. This is clearly seen when dose-dense schedules are used in patients with "platinum-resistant" tumors. Furthermore, there is some evidence that these categories of sensitivity and resistance are transferable to other drugs such as paclitaxel [17].

Single or Combination Chemotherapy?

Approximately 50 % of patients who relapse will fall into the group of "platinum-sensitive" relapse. Prior the mid-1990s, patients were re-treated with platinum alone or in combination with other drugs. The evidence that combination therapy

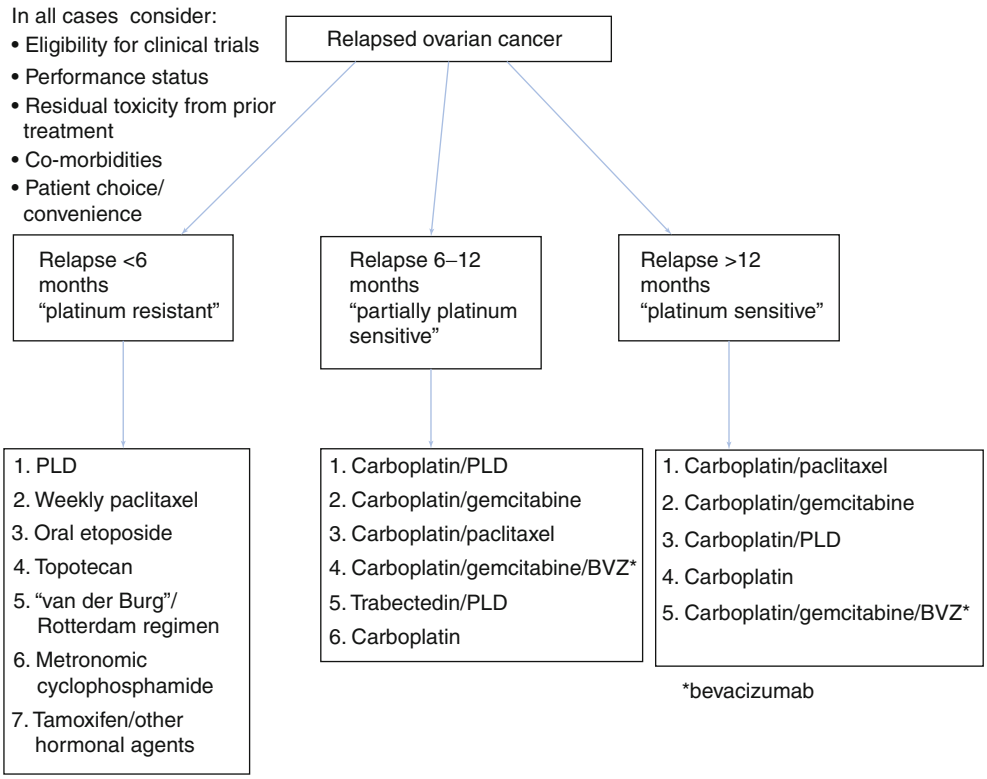

Fig. 10.1 Treatment pathways for relapsed ovarian cancer

was superior only emerged through a sequence of randomized trials. Differences in outcome were small, and it was only the large-scale trials that reliably showed a benefit for combination therapy. The first of these, ICON 4/AGO OVAR2.2, was performed in 802 patients who were randomly allocated to platinum-based therapy with or without paclitaxel. Over 90 % of patients were treated in the first relapse. There was a significant difference in progression-free and overall survival, favoring combination therapy, amounting to an absolute difference in the 1-year progression-free survival of 10 % and a 7 % difference in 3-year survival [18]. The effect of combination therapy on survival was seen irrespective of whether patients had previously received a taxane as first-line therapy. There was a trend for greater benefit in patients who had more than 12 months of platinum-free interval. The results were supported by a smaller randomized phase II trial from Spain in which 87 % of patients had previously received a taxane [19]. A second trial, AGO OVAR2.5, compared carboplatin with or without gemcitabine [20]. There was a significant improvement in tumor response rate and progression-free survival in patients receiving combination therapy. The progression-free survival was 8.6 months compared to 5.8 months (HR 0.72; $p=0.003$). This difference was similar to the ICON 4 trial (HR 0.76; $p=0.0004$). However, no difference in survival was seen. It has been argued that the two trials contained different populations; more patients with "partially platinum-sensitive" disease were included in OVAR 2.5 compared to ICON 4 (40 vs. 25 %). Some clinicians preferred this combination to carboplatin and paclitaxel as there was no hair loss or neuropathy. However, myelosuppression (in spite of the lower dose of carboplatin AUC 4) is unpredictable and can sometimes limit dosing and scheduling of this regimen.

Concern about the toxicity of carboplatin and paclitaxel was one of the reasons for exploring carboplatin and pegylated liposomal doxorubicin (PLD). The multinational CALYPSO trial compared this combination with carboplatin and paclitaxel. The study, designed as a non-inferiority trial, enrolled 976 patients with platinum-sensitive ovarian cancer relapsing more than 6 months after first- or second-line therapy. The combination of carboplatin and PLD was superior with respect to progression-free survival (HR 0.82; $p=0.005$). The median PFS was 11.3 months compared to 9.4 months [21]. However, it should be noted that some of these effects may be due to more or longer treatment with carboplatin and PLD. More patients treated with paclitaxel stopped treatment before six cycles, more commonly due to toxicity than progression. Nevertheless, the major difference in toxicity profile is a significant advantage of carboplatin and PLD. In particular, carboplatin hypersensitivity, a relatively common event seen when re-treating women with ovarian cancer, was reduced by half in patients receiving carboplatin and PLD. There was no difference in survival [22]. The regimen is popular, and PLD is more commonly used in the platinum-sensitive group rather in patients with "platinum-resistant" disease. Opinion remains divided about the choice of treatment in women who relapse more than a year

after first-line therapy as the data from ICON 4 are still the only results showing a survival advantage for combination therapy. There are now three combination regimens to choose from, but it is unclear whether the sequencing of different drugs has any effect on outcome. This is being studied in an Italian-led trial MITO 7, in which patients are randomized to a sequence of either PLD followed by carboplatin and paclitaxel or the same combination followed by PLD at progression.

"Partial Platinum Sensitivity": Is There a Place for Delaying the Reintroduction of Platinum?

Some uncertainty exists about the best choice of treatment in this group: Principally should platinum be used or could it be safely deferred until a later point in treatment? The results of the OV301 study in which PLD was used either alone or in combination with trabectedin, a DNA minor groove-binding drug, showed that in the "partially platinum-sensitive" subgroup, there was a significant survival benefit for the combination group [23, 24]. The hypothesis from this trial is that delaying the reintroduction of platinum, extending the "platinum-free interval," leads to a better response to platinum on subsequent relapse [25]. The concept is now being examined in the INOVATYON trial that will randomize patients to either carboplatin and PLD or trabectedin and PLD with planned carboplatin and paclitaxel therapy in the latter group at subsequent progression.

Platinum Resistance

"Platinum-resistant" ovarian cancer is not only an empirical definition but also a heterogeneous term encompassing patients who progress during treatment (refractory) or within 6 months of (platinum-based) treatment. The clinical behavior of tumors relapsing after first-line therapy is often very different to progression after multiple lines of treatment. Some patients have a rapidly progressive deterioration in health while in others tumor growth is much slower. Decisions about treatment need to take account of this, but most clinical trials do not differentiate between these different biological behaviors.

The mechanisms underlying platinum resistance are complex and not particularly well understood in the clinical environment. It is influenced by a variety of factors such as altered drug uptake, efflux, metabolism, increased repair of DNA damage, or reduced ability to undergo apoptosis [26]. At present there is no reliable test to guide clinical decision-making. There are several candidate markers such as low levels of the DNA repair enzyme, ERCC1, and aberrant PI3K/AKT signaling pathways. Measurement of the DNA repair enzyme ERCC1 has been extensively studied in lung cancer [27]. Low levels are associated with better survival and sensitivity to platinum [28, 29]. It has been more difficult to demonstrate this relationship in ovarian cancer [30–32]. Deficiency of homologous recombination repair of DNA, found in patients with germ-line BRCA gene mutations and a number of other somatic mutations, is a marker of platinum sensitivity. The restoration of HR competency is associated with platinum resistance. It is likely that in the future molecular profiling of tumors will provide better evidence of the likelihood of platinum resistance. For now, clinicians continue to use the empirical definition of platinum resistance, although as will be shown below, many patients with platinum resistance will have a tumor that responds quite well to further treatment with platinum. Perhaps at the moment, it would be better to define true platinum resistance as progression during platinum therapy. This would fall within the current definition of platinum-refractory ovarian cancer, which is the absence of a partial response to platinum or tumor progression during chemotherapy.

What Are the Drug Choices for "Platinum-Resistant" Ovarian Cancer?

In spite of the caveats in defining platinum resistance, most women are treated with non-platinum drugs, usually given as a single agent. These include liposomal doxorubicin (PLD), topotecan, oral etoposide, gemcitabine, and paclitaxel. In this setting, the response rates are low ranging between 10 and 30 %. Treatment decisions are usually dependent upon patient fitness, residual toxicity from prior chemotherapy, previous chemotherapy drug history, convenience, drug side effects, quality of life, and availability of appropriate clinical trials. There is no evidence from randomized studies that combination therapy is superior to single-agent therapy.

Although there is no consensus in the treatment of platinum-resistant tumors, many clinicians consider PLD as a reasonable first-line treatment option although its increasing use in combination with carboplatin for "platinum-sensitive" relapse are likely to alter practice. Its activity in phase II trials [33, 34] is only modest, and although the randomized trial comparing PLD with topotecan showed benefit in progression-free and overall survival, there was no evidence of superiority of PLD in the platinum-resistant subgroup [35]. However, the greater hematological toxicity of topotecan and its scheduling, daily for 5 days every 21 days compared with 4-weekly administration, are a disadvantage. Patients may tolerate weekly scheduling of topotecan, but the outcome data are no better and possibly inferior to standard scheduling of the drug [36]. Furthermore, a recent comparison of topotecan with weekly paclitaxel alone, or in combination with carboplatin, showed no difference in the progression-free survival. Toxicity was greatest

Table 10.1 Chemotherapy treatment options in platinum-relapsed ovarian cancer

Trial	*N*	Treatment	Phase	Patient population	Comments
ICON4 [18]	802	Carboplatin/paclitaxel	Phase III	Platinum sensitive	
AGO-OVAR 2.5 [20]	356	Carboplatin/gemcitabine	Phase III	Platinum sensitive	
CALYPSO [44]	976	Carboplatin/PLD	Phase III	Platinum sensitive	
OVA 301 [23]	672	PLD/trabectedin	Phase III	Platinum sensitive and resistant	In partially platinum-sensitive patients, this regimen may be used to prolong platinum-free interval
OCEANS [45]	484	Carboplatin/gemcitabine and bevacizumab	Phase III	Platinum sensitive	
AURELIA [46]	361	Topotecan, pegylated liposomal doxorubicin, or weekly paclitaxel plus bevacizumab	Phase III	Platinum resistant	
"van der Burg"/"Rotterdam" regimen [47]	107	Weekly cisplatin plus oral etoposide followed by maintenance etoposide	Phase II	Platinum sensitive and resistant	6 weekly IV cisplatin (50–70 mg/m^2) infusions on days 1, 8, 15, and days 29, 36, 43 Daily oral etoposide 50 mg on days 1–15 and days 29–43 Maintenance oral etoposide 50 mg/m^2 per day for 21 days, every 4 weeks, for 6–9 cycles
"Leuven" dose-dense chemotherapy [48]	33	Carboplatin AUC 4 and paclitaxel 90 mg/m^2 d1, d8 q 21	Phase II	Platinum sensitive and resistant	
Havrilesky et al. [49]	29	Carboplatin AUC 2 and paclitaxel 80 mg/m^2: days 1, 8, and 15 on a 28-day cycle.	Phase II	Platinum sensitive and resistant	
Markman et al. [38]	48	Weekly paclitaxel (80 mg/m^2)	Phase II	Platinum resistant	

with combination therapy [37]. Increasingly, weekly paclitaxel is used in patients with platinum-resistant recurrence. Several phase II trials have reported activity of this regimen [38–40] although a small randomized trial comparing weekly with 3-weekly therapy failed to show any benefit. Nevertheless, the emerging data from both metastatic breast cancer [41, 42] and first-line therapy of ovarian cancer [43] strongly suggest that this schedule is superior. However, it is not clear how the drug will be used in the future if weekly paclitaxel becomes adopted as a standard treatment for first-line therapy (see Table 10.1).

Gemcitabine monotherapy is an alternative option in platinum-resistant patients with response rates of up to 16 % observed [50]. A randomized phase III trial demonstrated similar response rates and progression-free survival for PLD and gemcitabine [51]. Gemcitabine has a different toxicity profile to PLD with its dose-limiting toxicity being myelosuppression with no neurotoxicity, PPE, or alopecia. Etoposide has been shown to be effective in the treatment of platinum-resistant ovarian cancer and as a monotherapy, response rates of up to 25 % have been seen [52].

Platinum-based therapy should also be considered in the "platinum-resistant" group of tumors. A tumor response rate of 46 % in platinum-resistant patients using "dose-dense" cisplatin and etoposide therapy followed by maintenance with oral etoposide [47] has led to a number of other phase II studies of dose-dense platinum-based therapy with paclitaxel [53, 54]. Patient selection may have had an influence on the results; some of these treatments have significant toxicity and require patients to attend weekly for some of their treatments.

Toxicity needs to be considered in all patients with recurrent disease and in particular those in whom the benefit of chemotherapy is likely to be modest. Simple nontoxic chemotherapy regimens such as metronomic cyclophosphamide are being explored. The results of some studies, particularly in combination with bevacizumab, have been encouraging [55]. Careful monitoring of symptoms and quality of life is needed in order to establish these treatments in clinical practice.

Do Hormonal Treatments Have a Place in the Treatment of Recurrent Ovarian Cancer?

Ovarian cancer is known to express estrogen and progesterone receptors. However, unlike in breast cancer, hormone-driven treatment has not met with much success. A Cochrane review of tamoxifen in relapsed ovarian cancer reported a response rate of 9.6 % with a further 31.9 % achieving stable disease [56]. The definition of stable disease varied significantly within trials; thus, the robustness of this result is questionable. A number of small single-institution trials have reported response rates of up to 18 % in platinum-resistant ovarian

cancer [57, 58]. Aromatase inhibitors have also been studied in platinum-resistant ovarian cancer with similar results reported [59]. As these hormonal treatments are simple, oral, and well tolerated, it is a reasonable option in platinum-resistant patients where all other therapies have been exhausted and/or the patient has a poor performance status.

Molecular Targeted Therapies and Recurrent Ovarian Cancer

A better understanding of the molecular pathways involved in tumorigenesis has led to the development of a large number of novel molecular targeted drugs. Many of these are now in advanced stages of clinical development. The emerging results of these trials are encouraging, but the greatest challenge may yet lie ahead in positioning these drugs at the most effective point of the treatment journey of ovarian cancer patients. The considerable cost of these drugs will also pose difficulties in funding particularly as no biomarkers have been identified to select patients who are likely to benefit.

Targeting Angiogenesis: How and When?

The angiogenic pathway is a critical component of tumor growth and metastasis. Targeting angiogenesis is of particular relevance in ovarian cancer, and numerous antiangiogenic drugs have been developed. Bevacizumab the humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF-A) is the most widely investigated antiangiogenic agent. The greatest activity of bevacizumab as monotherapy has been observed in ovarian cancer. Two phase II trials of single-agent bevacizumab reported response rates of 21 % [60] and 16 % [61], respectively. These results are particularly interesting as two-thirds of the patients had received two or more lines of chemotherapy, and 42 % were classified as "platinum resistant" in the GOG 170-D trial. In the second multi-institutional study, all patients were deemed platinum resistant. However, this study was terminated early due to the unexpectedly high rates of gastrointestinal perforations (11 %). Despite this, bevacizumab clearly exhibited significant activity with a median progression-free survival of 4.4 months. A third phase II study of bevacizumab plus low-dose metronomic cyclophosphamide also reported a significant clinical benefit in relapsed ovarian cancer with a response rate of 24 % [55]. A lower but still significant gastrointestinal perforation rate was seen in this study.

Adverse effects of bevacizumab are now well defined and include hypertension, proteinuria, arteriovenous thromboemboli, and gastrointestinal perforation. The risk of GI perforation appears to be associated with a greater number of previous lines of chemotherapy, extensive bowel involvement with tumor, and possibly bowel resection [62]. The initial concerns about excessive toxicity have largely abated, and bevacizumab trial protocols have included comprehensive guidelines on managing these toxicities.

Bevacizumab is now licensed in Europe for second-line treatment of ovarian cancer as it has been shown to be beneficial in patients with "platinum-sensitive" recurrent ovarian cancer. In the OCEANS trial, the addition of bevacizumab to carboplatin/gemcitabine followed by maintenance bevacizumab significantly improved response rates (79 vs. 57 %; $p<0.0001$) and prolonged progression-free survival (12.4 vs. 8.4 months; HR 0.484; $p<0.0001$) [45]. The results of a similar study, GOG 213, using carboplatin and paclitaxel are awaited.

In platinum-resistant ovarian cancer, the AURELIA study demonstrated efficacy of bevacizumab plus standard chemotherapy (topotecan, pegylated liposomal doxorubicin, or weekly paclitaxel) [46]. The risk of progression was halved with a median progression-free survival of 6.7 months compared to 3.4 months in women who received chemotherapy alone (HR 0.48: $p<0.001$). In addition, patients who received bevacizumab had a significantly higher response rate (30.9 vs. 12.6 %, $p=0.001$). This is the first study to show a benefit of a targeted agent in platinum-resistant ovarian cancer, and the overall survival results are awaited with interest.

With four positive phase III trials in ovarian cancer, bevacizumab has undoubtedly been established as an important drug in the treatment of ovarian cancer. However, many unanswered questions remain: Should bevacizumab be used in first-line therapy or reserved for "platinum-sensitive" or indeed "platinum-resistant" relapse? The drug is expensive, and more work needs to be done to determine the optimum duration of therapy dose of drug. None of the studies have yet shown definite survival benefits, and the implications of treatment that lead to an improvement in PFS without necessarily increased OS need to be considered.

As the population of patients exposed to bevacizumab grows, there is also a pressing need to investigate whether patients can be re-treated with bevacizumab at relapse and/or on development of platinum resistance.

What Is the Role of Small-Molecule Tyrosine Receptor Kinase Inhibitors in Ovarian Cancer?

Several oral small-molecule VEGF receptor tyrosine kinase inhibitors have been tested in patients with recurrent ovarian cancer. Pazopanib and nintedanib, multi-targeted small-molecule tyrosine kinase inhibitors targeting VEGFR and PDGFR (platelet-derived growth factor receptor), have demonstrated activity in recurrent ovarian cancer by delaying progression [63, 64]. First-line studies with these oral agents are already in progress, and these agents need to be evaluated in recurrent ovarian cancer. One example is the ICON 6 trial

with cediranib, an inhibitor of VEGFR in patients with "platinum-sensitive" first relapse. Recruitment to this phase III placebo-controlled three-arm study of chemotherapy with concurrent and maintenance cediranib has been completed, and results are expected in 2013.

Which Other Receptors and Cellular Pathways Are Being Targeted by New Molecular Therapeutic Agents?

PARP Inhibitors

A great deal of interest has been generated by the results of phase II trials of PARP (poly(ADP-ribose) polymerase) inhibitors in ovarian cancer. PARP proteins are implicated in a wide range of cellular processes and most significantly in DNA repair pathways. Inhibition of the PARP enzyme can lead to an accumulation of double-strand breaks and cell death. The BRCA 1 and 2 proteins play critical roles in homologous recombination repair of DNA damage, and mutation or suppression of BRCA genes impairs HRD and leads to lethal DNA damage in the presence of PARP inhibitors that block alternative repair pathways [65, 66]. Germ-line mutations in BRCA 1 and 2 are present in up to 22 % [67] of women with ovarian cancer. Up to 50 % of high-grade serous ovarian cancers may exhibit "BRCAness," a phenomenon by which patients with sporadic ovarian cancer behave similarly (e.g., response to platinum, improved survival and response rates) to patients with inherited BRCA mutation ovarian cancer [67–69]. These tumors have defects in proteins involved in homologous recombination. The use of PARP inhibitors therefore has potential for a wider therapeutic index than originally thought.

Most of the published data are from trials with olaparib, one of the now many PARP inhibitors undergoing study in recurrent ovarian cancer. Single-arm phase II trials have shown that olaparib is active in both patients with germ-line BRCA-mutated ovarian cancer and in sporadic ovarian cancer that maintains "platinum sensitivity" [70, 71]. However, a small randomized trial comparing PLD with olaparib in patients with germ-line BRCA-mutated ovarian cancer showed no difference in progression-free survival [72], largely because the response to PLD was unexpectedly high in this group of patients. Two randomized trials that included patients with BRCA-mutated and sporadic ovarian cancer have shown significant improvement in progression-free survival when olaparib is given as maintenance therapy in patients responding to platinum-based therapy [73] or combined with chemotherapy and then continued as maintenance therapy [74]. Olaparib was well tolerated with mainly grade 1 and 2 toxicities reported of fatigue, nausea, and anemia and can be successfully administered for long periods.

It is clear that this group of drugs is highly active in patients with BRCA-mutated ovarian cancer and also has activity in sporadic high-grade ovarian cancer. BRCA dysfunction whether through mutation or gene methylation is a marker for HRD, the key defect resulting in sensitivity to PARP inhibitors, but there is currently no test for HRD. Better identification of susceptibility to PARP inhibitors in patients with sporadic ovarian cancer is needed. PARP inhibitors will without doubt become an important class of drugs in the treatment of ovarian cancer, but none have yet been licensed for treatment. Ongoing research will help to define the optimum position of these drugs in the treatment of women with ovarian cancer.

EGFR Inhibitors

The epidermal growth factor receptor (EGFR) is involved in cellular proliferation, differentiation, and metastasis. EGFR is overexpressed in up to 70 % of ovarian cancer patients [75], and preclinical data suggested EGFR would be a good target for ovarian cancer. A number of monoclonal antibodies directed against EGFR (trastuzumab, cetuximab, pertuzumab, panitumumab) and small-molecule tyrosine kinase inhibitors (gefitinib and erlotinib) have been investigated in ovarian cancer. It is likely that responses are dependent on the presence of a mutation in the catalytic domain of the EGFR receptor [76]. To date results for EGFR inhibitors in ovarian cancer have been disappointing, and recently a large phase III trial of erlotinib as maintenance treatment in first-line ovarian cancer has also reported negative results [77]. No benefit was seen in any subgroup including those with known EGFR mutations. Following the results of these trials, further development of EGFR inhibitors in ovarian cancer is uncertain at present.

Targeting the α-Folate Receptor, a Tumor Marker for Ovarian Cancer?

Folate receptor α (α-FR) is upregulated in the majority of epithelial ovarian cancers and correlates with grade and stage of tumor [78]. α-FR is rarely expressed in normal tissues thus making it an attractive target. Farletuzumab, a humanized monoclonal antibody to α-FR, has demonstrated encouraging activity in combination with carboplatin and paclitaxel in platinum-sensitive relapsed ovarian cancer [79]. Subsequently, two phase III trials have been conducted in recurrent ovarian cancer. The first trial of farletuzumab in combination with carboplatin/paclitaxel randomized over 1,000 patients with platinum-sensitive ovarian cancer. The second smaller trial has been conducted in platinum-resistant patients, with farletuzumab in combination with weekly paclitaxel. Results from both trials are awaited. In an alternative approach, a folate-receptor-targeting molecule has been conjugated through a chemical linker to the target, vintafolide (EC145), a vinca alkaloid selectively to ovarian tumors.

By linking the targeting agent to ^{99}Tc radiopharmaceutical etarfolatide (EC20), it has been possible to image tumors overexpressing the folate receptor. The results of the first randomized trial combining EC145 with PLD have been encouraging [80], and a phase III trial is in progress.

Other Molecular Targeted Agents

It is clear that ovarian cancer does not result from a single mutation or aberrant pathway but occurs following defects in multiple oncogenic pathways involved in cell growth, proliferation, metastasis, and apoptosis. In addition to the above, other drugs, such as those targeting insulin-like growth factor-1, inhibitors of Src kinase, mTOR, and PI3 kinase pathways, are being developed. These studies are at an early stage of development. A number of these agents are likely to show activity in recurrent ovarian cancer. However, a novel approach to the design of clinical trials is needed; otherwise, many years will be spent testing individual agents without fully knowing how to position these treatments in clinical practice.

Conclusions

Treatment of recurrent ovarian cancer presents clinicians and patients with a many therapeutic choices. Treatments prolong life and new drugs are likely to extend survival further. Surgery in subgroups of women may add further to the control of disease, but decisions to perform surgery need to be based on a strong evidence base. This has been lacking, but current trials will help to identify which patients might benefit and the magnitude of the effect of surgery. Progress in the use of chemotherapeutic agents over the last decade has been followed by clear evidence of the benefit of several molecular targeted agents in ovarian cancer. The choices are increasing but many challenges lie ahead, particularly how to identify the patients most suitable for these therapies and how to position these treatments in the management of recurrent ovarian cancer.

Concluding Comments

- Surgery for ovarian cancer is possible in some patients, but its value in prolonging disease control remains uncertain. Ongoing clinical trials will help to answer these questions.
- "Platinum sensitivity" remains a useful definition for treatment choices, but the definition of "platinum resistance" is less secure, and better methods are needed to help select the most appropriate treatment for these patients.
- Therapies directed at several molecular targeted pathways are showing great promise. The challenge is to integrate these into clinical practice, and this can only be done effectively by identifying predictive markers to help select patients for the appropriate treatment and using novel trial designs to help position these new drugs in the pathway of clinical care.

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How to Study Rare Gynecological Tumors: Trials or Registries?

11

Isabelle Ray-Coquard and David M. Gershenson

Summary Points

- Funding is limited, the pharmaceutical industry has little incentive to develop drugs for rare cancers, and patient accrual to trials is frequently prolonged.
- There is no consensus on "standard" management and the most efficient clinical trial design methodology, and national regulatory requirements currently significantly impair the ability to conduct international trials.
- Two organizational aspects (registries and pure clinical trials) need to be described and challenged in terms of advantages and disadvantages.
- A combination of both organizations is probably a good compromise to optimize research in rare gynecologic cancers.

Introduction

With 16.1/100,000 new EU annual cases, rare gynecological tumors (RGTs), including ovarian, fallopian, uterine, cervical, vaginal, and vulvar, represent more than 50 % of all gynecologic cancers and frequently affect young patients [1]. However, each of these tumors is so rare that natural history, prognostic factors, and definitive histological diagnosis are not clearly defined. The extreme variability of patients (age, histologic subtypes, localization, stage) makes treatment strategies multiple and complex. Too rare to be analyzed through big randomized trials, treatments have been developed based on expert opinion or from therapeutic advances made against other similar tumors but using fragmented retrospective data. Difficulties in histological diagnosis, and absence of clear prognostic factors and evidence-based medicine being not applicable for medical decision making, makes the treatment of RGT challenging, and only dedicated multidisciplinary staff with a systematic pathological review by expert pathologists can adequately manage these diseases [2]. Moreover, research (clinical and biological) and management (surgery, radiotherapy, systemic treatments) of patients differ and are not optimal [3]. Harmonization of research activities and of medical practices and the education of all professionals are therefore essential to improve disease knowledge and management worldwide. In spite of the fact that oncologists and gynecologists managing RGT are usually well organized at a national level, there are no specific structured collaborations that exist internationally.

With regard to clinical research, if we make a parallel with other rare cancers such as sarcoma, the clinical presentations at the sarcoma session at the American Society for Clinical Oncology (ASCO) in 2011 were perhaps most remarkable for the inclusion of data from five randomized clinical trials including 1,867 patients, of whom 837 had metastatic disease. Two studies reported an improvement in progression-free survival (PFS); however, an overall survival benefit was not achieved in any of all these studies in part explained by the inclusion of too heterogeneous group of different patients and probably diseases [4, 5]. As an investigative community, we must come to terms with the most efficient clinical trial designs to study drugs to more rapidly allow specific patients' access to the most active drugs for their diagnosis.

In rare cancers, the problems are distinct from that of more common cancers. Although ~35 % of cancer deaths arise from the rarest 20 % of cancers, such as sarcomas, we still do not have efficient mechanisms by which drugs can be studied and moved through the approval process. The phar-

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maceutical industry is reluctant to investing in the treatment of "niche" diseases with small market potential [6]. The scientific review process in academic centers is burdened by studies that may only accrue one or a few patients with a rare diagnosis in a year, and regulatory requirements are greater than ever in clinical trial conduct [7].

According to the National Institutes of Health's Office of Rare Diseases, in the United States, "rare" diseases are defined as those having a prevalence of 200,000 individuals or less [8]. Such a definition actually encompasses several different gynecologic malignancies. Historically, funding for research on rare cancers had been extremely limited. Additionally, pharmaceutical companies had little incentive to develop drugs for rare cancers.

Over the past three decades, national initiatives have heightened the awareness and impact of rare cancers. In 1983, the Orphan Drug Act was enacted, providing pharmaceutical firms with incentive for sponsoring clinical trials of rare diseases [9]. In 1993, in the United States, the Office of Rare Diseases Research (ORDR) was established within the Office of the Director of the National Institutes of Health. Its purpose has been to stimulate and coordinate research on rare diseases. In 2002, Congress passed the Rare Diseases Act, the purpose of which was to increase federal funding for diagnostics and treatment for patients with rare diseases [10]. Then, in 2009, the Division of Cancer Prevention held a workshop that concluded with several recommendations related to (1) biospecimens, (2) Centers of Excellence for Rare Cancers, (3) funding, (4) comprehensive knowledgebase, (5) animal models, (6) current technology and development of new detection and prevention methods, and (7) an increased role for patient advocacy groups [11]. In 2011, the Institute of Medicine published its report *Rare Diseases and Orphan Products: Accelerating Research and Development* [12]. This report called for implementing an integrated national strategy to promote rare diseases research and product development.

What are the approaches that can be considered to improve the chance of success in clinical trials in the near future? We are already observing examples where new paradigms are blossoming. The use of specific signatures of tumors, rather than a histological diagnosis, may have a great impact on the conduct of clinical trials in the future. Good examples are the successes of VEGF-directed therapy in renal cell carcinoma; imatinib mesylate in CML, GIST, and rarer diagnoses; crizotinib in ALK+ non-small cell lung cancer; or vemurafenib in V600E BRAF mutant melanoma to see that screening a large number of patients for genetic or other tumor markers and treating only the affected population may be the most effective design to get to the end point of clinical success.

Of importance of course is how many relevant targets will be found in common and rare cancers. Perhaps half of non-small cell lung cancers do not have a defined oncogenic "driver," much as seems to be the case for uterine leiomyosarcoma or carcinosarcoma. Trials that focus on mechanisms, rather than histology, are one possible means to overcome the concern about rare versus common cancers and to have an eventually greater chance of trial success. The open-access movement also provides ample reason to be excited about collaboration on rare cancers such as sarcomas. In a similar way, anonymized clinical or radiological data can provide a very useful resource to help choose a therapeutic option using collective experience. Finally, all these comments confirm the need for global databases dedicated to rare cancer able to confirm diagnosis, to access clinical data and tumor material, and so to drive research on molecular biology rather than only localization and histology.

The Case for Prospective Databases Registries

To compensate for the rarity of some ovarian tumors, in 2002, a French language website was created in order to inform patients and their families and keep an update of scientific and bibliographic knowledge of rare tumors of the ovary [13] (Fig. 11.1). Information on the existence of such a tool has been presented at different French gynecology/oncology meetings since 2002, and the project has received financial support from the French government since 2005. The forum is accessible to all physicians in charge of these rare neoplasms, whether to ask for or to provide advice. In a first step, specific clinical research programs dedicated only to germ cell tumor (GCT) and sex cord-stromal tumors (SCT) were developed on the website in order to confirm the feasibility of this system. In addition to offering French physicians' best-practice advice on the diagnosis and the surgical and medical management of these patients, the objective was to develop a clinical research program with health professionals in order to accumulate clinical and biological information on the natural history and prognosis of these tumors. It was also aimed to organize a central review of tumor samples. Finally, a study of long-term toxicities of chemotherapy and surgery was initiated and also the monitoring of posttreatment fertility. Physicians, identified by their registration number at the National Medical Association, register online and receive confidential log-in information to access the database. Then, they can include rare ovarian cancer patients and enter information about these patients in the online expert advice forum. Brief information about patient characteristics, diagnosis, and, if applicable, first surgery is collected and used for online expert advice.

Between March 2002 and June 2009, 180 patients from all over France were included in the SCT and GCT programs;

Fig. 11.1 Experience of national registries dedicated to rare cancers: French Rare Ovarian Cancer Network. Website coordinated and designed by the first author

for 25 % of them, a second opinion was sought from the online expert panel. Most patients were included by medical oncologists particularly involved in clinical trials ($n=84$) or not ($n=71$), or by surgeons ($n=25$). Of 100 patients initially screened and included, 77 patients were eligible for second opinion. This first analysis confirms several important hypotheses concerning the management of rare ovarian cancers. Firstly, with a 37 % discrepancy rate between initial diagnosis and second opinion, the results demonstrate that the pathological diagnosis of these rare entities requires expertise and centralized review. Secondly, the subgroup analysis of SCT and GCT patients registered to the website confirms the heterogeneous medical practice of surgery and chemotherapy. However, whether a website dedicated to rare tumors can improve medical practice or just be used to collect patient cases remains to be clarified. Indeed, 50 patients by subgroups are needed to explore medical practices at a national level [14]. This opens the debate about the "pros" and "cons" of the website: "pros" suggest that more information can be conveyed to practitioners for better patient management, whereas "cons" maintain that more support should be given to some specialized centers to significantly improve the efficiency of clinical management. Again, it seems too early to gain conclusive evidence from this exclusive experience. By nature, studies of rare tumors are often hampered by limited or nonuniform data because they encompass multiple histological subtypes and multiple medical strategies. As a result, making firm recommendations based on the findings of such studies can be difficult [15]. The present study highlights the ability of website registration to serve as a basis for developing biological and clinical research trials on rare tumors and to establish adapted clinical guidelines. For example, biological or immunohistochemical factors are under study, notably for SCT. Granulosa cell tumors of the ovary can be identified based on morphological, biochemical, and molecular criteria [16]. In order to understand the molecular pathogenesis of these tumors, different activating mutations of the signaling pathways are under consideration using tumor samples ($n=260$) collected within the clinical research program from the website. These samples represent

a unique opportunity, since the diagnosis of granulosa cell tumors has been confirmed and all patients have received similar management (adapted to disease stage and other prognostic factors) and appropriate follow-up allowing comprehensive analysis of biological factors. A better characterization of signaling pathways known to be important in the regulation of granulosa cell growth and differentiation could lead to the identification of new targets for treatment and, consequently, new opportunities for targeted treatment for these rare tumors.

The rate of study inclusions after 5 years seems to confirm the website's ability to help organizing clinical research on rare tumors at a national level and stimulate patient recruitment. In addition to firm clinical data on prognosis and management, physicians need rapid answers to the questions they are faced with when dealing with these patients, especially young patients with good prognosis and a desire of preserving fertility. The website, which provides accurate online information and a bibliography and runs a discussion forum dedicated to these tumors, appears relevant to this particular issue. While providing both patients and physicians with rapid access to information on these rare neoplasms, this experience also enables the progression of clinical research and the centralized accumulation of data with the aim to further improve the management of these young patients.

Given the rapid success of this experience with patients and physicians, in 2010, the scientific board decided, with a substantial financial support from the French Cancer Institute (INCa), to broaden the scope of the website within a national rare gynecologic cancer network including several "referent regional cancer center" to offer information and develop a database and dedicated cancer management on all other rare ovarian tumors such as borderline carcinoma, small cell carcinoma, mucinous and clear cell carcinoma, and other very rare tumors. The goals remain the same, namely, the provision of a helpful tool for diagnosis and treatment and the development of specific clinical and biological trials for these rare tumors but including "regional centers" able to be a relay between local management of the patients and national organization. Twenty-one regional centers agree to participate around the coordination by three national centers. Main objectives were to monitor the management of rare gynecologic cancer and give equal access to expertise (systematic second opinion for histological diagnosis) and innovative treatments (within dedicated clinical trials to all patients with these tumors). Seven hundred and twelve patients benefited from second opinions and were included by the expert pathologists of the network, representing 71 % of expected incident cases. Major discordances concern 9 % of patients. Two hundred and ninety-four patients gave informed consent and were included in the clinical database during the 2011 period; 85 (29 %) had SCT, 57 GCT, 61 BLT, 26 MC, 20 CCC, and 45 other. Two hundred and eighty (96 %) patient cases were discussed in dedicated MS. Patients were included in the website before initial treatment in 229 (78 % of cases) or at the time of the first relapse (22 %). Eighteen patients could be included in a clinical trial. Virtual tumor banking is ongoing to develop molecular diagnosis (as FOXL2 for SCT). This web-based tool supported by a national network including national and regional expert centers seems to be an efficient tool for the organization of the management of rare ovarian cancer [17]. However, in the databases, only ten patients were finally included in clinical trial in 2011. There remains the problem of the availability of new drugs for these patients (not only in first line but also at relapse). In Europe, accrual in phase II or III trials conducted at the national level might not be high enough to confirm clinical benefits in patients with rare tumors. International studies should be developed to enhance patient accrual and improve both clinical knowledge and management.

In total, RGTs represent more than 50 % of the total number of gynecological tumors with about 80,000 new cases per year in Europe, involving more than 30 different histological diagnoses, with a very limited number of patients in each diagnostic category. At present, RGTs benefit from the advances made for other cancers, but do not have any evidence-based guidelines guaranteeing adequate management or appropriate therapeutic approaches. Treatment networks are well structured at the national level, but no consensus exists at the EU level. Registries have been initiated by national groups, but many are limited to specific cancers. A European program is under development (GYNET) and will provide the first steps towards better and specialized management of RGT while promoting the conditions to allow top-level clinical research by providing a critical mass of patients. The availability of an Internet-based, shared platform for information dissemination on RGT will enhance patient and patients' association information, setting the basis for early detection and better management. In the medium term, the harmonization of practices will reduce inequalities of management across the partnership but also at the EU level through the future opening of the network to additional countries. The platform will enhance new knowledge, through the harmonized analysis of data collected under common criteria. The GYNET network will include research and or educational organizations involved in the field of RGT, such as the national groups dedicated to gynecologic cancers from Italy (MITO), the United Kingdom (MRC), Germany (AGO), Belgium (BGOG), and France (GINECO). The project will rely on two kinds of web-based tools: national portals and a European platform. Those tools will be working as mirrors, at two confidentiality levels: a first level structured as a showcase website proposing information and knowledge sharing capacities and including a pathology description from a list of national experts' centers,

a national network information page when developed, and an accessible clinical trial list. On a second level, platforms will provide anonymous harmonized patient clinical data and a critical mass of data regarding specific settings to foster clinical trials and to develop specific targeted treatment or epidemiology tools for these rare tumors. National databases will be linked to the central database and automatically implement the data based on a secured data exchange protocol. The following outcomes are expected: improved information and knowledge directly leading to better diagnosis and outcomes. Clinicians will be trained according to the most efficient practices agreed by the consortium, improving their ability to manage patients. The result will be consolidation of a clinical database registry, available to clinicians and research groups to develop new and optimal clinical trials to define better treatment and therapeutic approaches of RGT and harmonization and best practices for better patient management. GYNET will offer a transposable model, to be extended to other countries, in the field of RGT or/and other pathologies. This approach is particularly necessary when facing the challenges of rare cancers.

The Case for Clinical Trials

The Gynecologic Oncology Group Initiative

Because of the perceived need for a sharper focus on rare gynecologic tumors, the Gynecologic Oncology Group (GOG) decided to establish a Rare Tumor Committee in 2005. At its inaugural meeting in July 2005, the 15 individuals present participated in a brainstorming session to begin to develop a consensus around rare gynecologic tumor research. At this point in our history, several forces were converging to catalyze enhanced interest in this area: (1) our understanding of the genes and signaling pathways involved in the pathogenesis of several rare gynecologic cancers was expanding; (2) bolstered by advances in genomic technology, molecular pathology studies were beginning to characterize the distinct molecular signatures of a number of these rare cancers; (3) hypothesis-generating clinical reports of rare gynecologic cancers increasingly emerged; and (4) the National Cancer Institute and, more specifically, NCI's Cancer Therapy Evaluation Program (CTEP) began to express a greater interest in supporting studies of rare cancers.

At that initial meeting, the group discussed the definition of "rare" gynecologic cancers and which tumor types might be optimal targets for protocol development, agreed upon the need for adequate resources and authority to launch this initiative, emphasized the importance of partnering with patient advocacy groups, and underscored the need for intergroup and international collaborations to successfully complete these trials.

Early Challenges and Strategies

One of the first challenges for the GOG Rare Tumor Committee was to decide which tumor types should be prioritized for study. Fairly rapidly, the committee arrived at a consensus to study rare ovarian cancers (see below). Cervical and vulvar cancers fell under the purview of the GOG Cervix Committee. Uterine sarcomas and uncommon endometrial cancer histotypes were under the GOG Corpus Committee. In addition, prior to this time, all histological subtypes of ovarian, peritoneal, and fallopian tube cancers were treated on the same clinical trials in the first-line and recurrent settings as well as within the GOG Developmental Therapeutics Committee portfolio of novel agent trials.

The next issue was which trials would be feasible in terms of patient accrual. For example, trials for carcinosarcoma or small cell carcinoma of the ovary might be unfeasible, whereas trials for clear cell carcinoma might be more practical. Although historical GOG data by histological subtype was available for some clinical settings, several decisions had to be made without complete data.

Malignant ovarian germ cell tumors and ovarian sex cord-stromal tumors had always been segregated into their own clinical trials within the GOG. To continue this strategy was a simple decision. For the uncommon histological subtypes of epithelial ovarian cancer—clear cell carcinoma, mucinous carcinoma, and low-grade serous carcinoma—a decision to develop separate trials for each of these was more difficult. The GOG has made its reputation on completion of a series of large phase III trials for newly diagnosed women with ovarian cancer and phase II trials for patients with recurrent ovarian cancer. Excluding patients from these generic trials would obviously have an impact on accrual. However, resistance to this paradigm shift was eventually overcome.

For several decades, we have known that epithelial ovarian cancer comprises not one homogeneous but rather several histological subtypes based on tumor cell morphology. The major support for this change in direction has been the diagnostic, molecular, and clinical report studies over the past few years that have indicated that clear cell [6, 18–26], mucinous [24, 27–34], and low-grade serous carcinomas [35–41] are distinct from the most common subtype—high-grade serous carcinoma. This approach was subsequently validated by the Gynecologic Cancer Intergroup (GCIG) Consensus Conference on Ovarian Cancer in 2010 [42]. As a result, the GOG Rare Tumor Committee initially focused on development of clinical trials for clear cell carcinoma, mucinous carcinoma, low-grade serous carcinoma, and sex cord-stromal tumors.

The third challenge is related to clinical trial design in the study of rare tumors [43]. For rare tumor investigations, in general, accrual is a major barrier. Thus, the committee needed to make key decisions about which trials could be

completed within the GOG, which would require intergroup participation, and which might benefit from international collaborations. Additionally, the GOG paradigm of large phase III trials would not apply to the vast majority of these studies. Furthermore, from almost the beginning, there was tension concerning which trials should be single-arm phase II studies and which ones were feasible to randomize. Early in the committee deliberations, novel trial design was discussed extensively. High-quality historical data on most of these rare tumor types was lacking for most subtypes. There was a consensus that, if at all possible, we wanted to avoid completing a study and not being able to interpret adequately the findings, thereby leading to flawed decision making. Some of the problems with attempting randomized clinical trials in rare diseases are illustrated in a study conducted by Gallin et al. [44]. Obviously, when the treatment effects prove to be dramatic and clearly superior to historical controls, a randomized trial is not necessary. However, predicting that type of outcome is almost impossible. How large should the treatment effect be to declare success or to anoint a new standard in a nonrandomized setting? An intelligent selection of the appropriate end points is of the utmost importance.

The fourth challenge has been the myriad national regulatory issues that impede international clinical trials in rare tumors [45]. For example, most of the European countries have very different regulatory requirements. In addition, research sites outside the United States that collaborate on clinical trials funded by the US government must complete extensive documentation. Furthermore, data collection, pathology review, reporting of adverse effects, and data monitoring and auditing may differ markedly from one authority to another. Although there have been numerous conferences and meetings focused on harmonization of operational aspects of international clinical trial conduct, much greater attention to these barrier is warranted.

Why Not a Registry Rather Than Clinical Trials

At several meetings during 2008–2010, the GOG Rare Tumor Committee discussed the advisability of establishing a GOG Rare Tumor Registry. Initially, there was a consensus that, if a registry were established, it should collect only prospective data on patients who meet specific eligibility criteria and not simply retrospective data on a variety of treatments in patients with inconsistent data elements. Ultimately, however, a decision was made not to pursue such a registry. The major issues that informed that decision included the following: (1) Such an undertaking would be too labor-intensive and resource-intensive at a time when cooperative group resources were constrained. (2) The GOG had no prior experience in establishing such a registry, and such may have been difficult to implement. (3) There could be too great a degree of selection bias in patients enrolled in such a registry. (4) Local IRB requirements appeared to be a major barrier to establishing a registry.

The GOG Rare Tumor Committee Portfolio: The Early Years

The overarching principles that have governed clinical trial development within the Rare Tumor Committee have included feasibility; novel clinical trial design with careful selection of end points; inclusion of translational research end points, whenever possible; and selective inclusion of prospective pathology review for trial eligibility (the first GOG committee to do so). Within a few years of its inception, the committee implemented a Request for Protocol (RFP) Concept submission in an attempt to focus the committee direction based on its strategic plan.

Sex Cord-Stromal Ovarian Tumors

There are three protocols for sex cord-stromal ovarian tumors. GOG 187 is a phase II trial of paclitaxel for patients with recurrent sex cord-stromal tumors. It was activated in 2000 and just completed accrual in 2012. GOG 251, a phase II trial of bevacizumab for women with recurrent sex cord-stromal tumors, was activated in 2008 and has completed accrual of 36 patients. GOG 264, a randomized phase II trial of paclitaxel and carboplatin versus bleomycin, etoposide, and cisplatin (BEP) for newly diagnosed advanced-stage and recurrent chemo-naive sex cord-stromal tumors, was activated in 2010 and has thus far accrued 11 patients.

Clear Cell Carcinomas

Because clear cell carcinoma of the ovary is a more common ovarian cancer subtype in Japan than in Western countries, Japanese investigators have had a long-standing interest in this entity. Based on promising findings of a randomized phase II trial of first-line chemotherapy for ovarian clear cell carcinoma, a phase III trial (GCIG/JGOG3017) of irinotecan plus cisplatin versus paclitaxel plus carboplatin was conducted and recently completed accrual. Final analysis of this trial is currently pending.

GOG 254, a phase II trial of sunitinib for patients with recurrent clear cell carcinoma of the ovary, was activated in 2010 and has accrued 20 patients to date. GOG 268, a phase II trial of paclitaxel, carboplatin, and temsirolimus followed by temsirolimus consolidation as first-line therapy for stage III and IV clear cell carcinoma of the ovary, was activated in 2010 and has accrued 60 patients thus far. Most recently, this trial has been joined by the Japanese GOG (JGOG). Target accrual includes 45 patients from the United States and 45 patients from Japan.

Mucinous Carcinomas

GOG 241, a GCIG intergroup multicenter phase III trial of paclitaxel and carboplatin +/– bevacizumab versus capecitabine and oxaliplatin +/– bevacizumab as first-line chemotherapy in patients with mucinous ovarian or fallopian tube cancer, is an international trial that was activated by the GOG in 2010. Target accrual is 323 patients. To date 29 patients (12 in the United States and 17 in the United Kingdom) have been accrued.

This trial is actually two separate harmonized trials, the data of which will be combined for analysis. It has suffered from very slow accrual in both the United Kingdom and United States related to the extreme rarity of this histological subtype. In addition, there have been a number of other obstacles, including lack of third-party coverage of the use of off-label drugs in the United States in some instances and regulatory issues in the European Union related to differences in distribution of bevacizumab from one country to another.

Low-Grade Serous Carcinomas

GOG 239, a phase II trial of selumetinib (AZD6244) for patients with recurrent low-grade serous carcinoma, was activated in 2007 and completed accrual of 52 patients in 2009. This trial was the first GOG trial to include prospective pathology review as an eligibility criterion. A second trial with another MEK inhibitor, trametinib, is under development. The target date for activation is in mid-2013. This trial is currently designed as a phase II/III randomized trial of trametinib versus "standard therapy," which consists of an attending physician's choice of one of five chemotherapy or hormonal therapy agents. Importantly, it is planned as an international trial with collaboration between the National Clinical Research Network (NCRN) in the United Kingdom and the National Cancer Institute in the United States. It is also hoped that other cooperative groups, such as the EORTC, will consider joining this trial.

Malignant Ovarian Germ Cell Tumors

Since the establishment of the GOG Rare Tumor Committee, no protocols for malignant ovarian germ cell tumors have been activated. In its first 2 years, the GOG was in discussions with the Children's Oncology Group (COG) to collaborate on a protocol for surveillance for low-risk disease and compressed BEP for intermediate-risk disease. Unfortunately, this collaboration did not materialize. However, there is currently a new initiative for a new international protocol with participation of COG, GOG, and the United Kingdom's Children's Cancer and Leukemia Group. This trial is in the early stages of development and tentatively includes low-risk, intermediate-risk, and high-risk cohorts. If approved, the low-risk cohort will undergo postoperative surveillance.

Summary

The development of novel agents and novel therapeutic strategies is more challenging in rare tumors than in the more frequently encountered tumors. For this reason, an emphasis has been put on these cancers at different political levels, recently bringing together different stakeholders, aiming to solve the problem imposed by the rarity of these tumors to allow for new clinical developments. For clinical research, the unresolved problem also includes epidemiological aspects; identification of patients; the definition of the most efficient primary end point; the capability to delineate randomized trials; new statistical approaches such as crossover studies, Bayesian statistics, or even using the patient as her own control; the need for an intergroup setting with associated administrative costs and requirements; and last but not least the development of rigorous partnerships with pharmaceutical companies in this context [46]. In conclusion, when comparing the strategies of registry data versus clinical trials for rare tumors, carefully planned and executed clinical trials provide a much more precise method of identifying effective therapies while minimizing selection bias and inconsistent or inadequate information. To optimize the study of rare gynecologic cancers, a greater focus on harmonization and removal of barriers to achieve enhanced international collaborations and consortia will be necessary. To help us, an international collaboration was built. IRCI (International Rare Cancer Initiative) is a joint initiative between the National Institute for Health Research (NIHR) Cancer Research Network (NCRN) and Cancer Research UK (CR-UK) in the United Kingdom, the National Cancer Institute (NCI) in the United States, and the European Organisation for Research and Treatment of Cancer (EORTC). The aim of this initiative is to facilitate the development of international clinical trials for patients with rare cancers in order to boost the progress of new treatments for these patients. The initiative hopes to encourage the use of innovative methodologies to maximize the potential for answering research questions and to identify and overcome barriers to international trials to allow international collaborative trials to run smoothly. Criteria for inclusion in the IRCI program depend on the rarity: a fixed rarity cutoff is not applied, but as a guide, cancers with a total incidence of less than 2/100,000 have been considered for inclusion in the IRCI program. Occasionally, rare clinical scenarios have also been considered. To date, IRCI has excluded rare molecular subtypes of common cancers, simply because this embraces most of cancer. However, a rare molecular subtype could be considered if it is a distinct, prospectively identifiable rare subgroup with a strong rationale for separate research, rather than inclusion as a molecular stratum in a mainline trial. Lack of existing trials: IRCI exists to develop new trials where there is no (or minimal) existing trial data and no existing trial. It is not intended to

compete with (or boost) existing trials. Potential for an interventional trial

Priority is given to cancers with potential for an interventional—usually randomized—trial (not an audit, registry, or non-trial tissue collection). There need therefore to be research treatments of genuine interest for investigation and sufficient patients for an international trial to be feasible. Enthusiastic champions' enthusiastic commitment from investigators to propose trial ideas and act as principal investigators is essential. Today, gynecological "subgroup" has selected uterine sarcoma where two randomized trials (adjuvant setting for leiomyosarcoma leads by GOG and advanced stage for high-grade uterine sarcoma leads by EORTC) and one phase II dedicated to endometrial stromal sarcoma are under consideration and near to be open for inclusion.

Concluding Comments

- Clinical trials are major concerns to improve management and knowledge for rare gynecologic cancers.
- A greater focus on harmonization and removal of barriers to achieve enhanced international collaborations and consortia is necessary to optimize such clinical research.
- Intergroup setting with associated administrative costs and requirements is needed.
- The development of rigorous partnerships with pharmaceutical companies is required.
- National networks dedicated to rare gynecologic cancers able to manage databases and to organize at national- and regional-level research and clinical trials are fundamental.

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What Is the Best Treatment Model for Gynecologic Cancers? Does Centralization Help?

12

Claes Göran Tropé, Torbjørn Paulsen, Ayesha Saqib, and Craig Underhill

Summary Points

- Ovarian cancer patients that are operated on by gynecologic oncologist have improved survival and quality of life.
- Ovarian cancer patients operated at teaching hospitals compared to non-teaching hospitals have improved survival.
- The evidence for improved outcome with centralized surgery is lacking for other gynecologic malignancies than ovarian cancer.
- Most of the available evidence addresses ovarian cancer in developed countries

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What Is the Best Treatment Model for Advanced Epithelial Ovarian Cancer? Arguments for the Centralization of Services

Claes Göran Tropé and Torbjørn Paulsen

About 67,000 new ovarian cancers are diagnosed in Europe every year, with the highest incidence in the Nordic countries and the UK [1, 2]. Epithelial ovarian cancer (EOC) has the highest mortality rate of any other female cancer in the Western world [1], mainly because most patients present with advanced (stages III–IV) disease [3]. However, 5-year survival rates differ substantially across European countries, ranging from 26.5 % in Estonia to 51.4 % in Iceland for patients diagnosed between 1990 and 1994 [4]. The 5-year relative survival rate for patients with EOC in Norway has improved over time [5]; in a large historical database including data from the Norwegian National Cancer Registry, the age-adjusted relative survival increased from 22 % during the period 1954–1958 to 44.1 % during the period 2005–2009 [6, 7]. One reason for these variations across Europe might be the extent to which guidelines for surgery and chemotherapy is followed in different European countries [1, 8].

As early as the 1930s, Meigs demonstrated the therapeutic value of cytoreductive surgery [9]. Four decades ago, Griffiths [10] reported that reducing the residual tumor to less than 1.5 cm improved survival, and since then primary cytoreduction followed by chemotherapy has become the standard of treatment for patients with advanced EOC. A meta-analysis by Bristow et al. showed a 5.5 % survival benefit for every 10 % increase in completely debulked tumors [11], a finding which has been confirmed by others [12–14]. In a meta-analysis of three prospective randomized trials with a total of 3,126 patients, du Bois et al. [14] concluded that the largest patient benefit was complete tumor resection. Therefore, lack of any macroscopic residual tumor should be regarded as the aim of surgery in patients with advanced EOC [14, 15].

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It has been reported that the outcome of other types of cancer is better when the patients are treated in specialized centers [16–19], and several studies have shown that the survival of patients with advanced EOC improves when their surgery is performed by a gynecologic oncologist rather than by a general gynecologist or general surgeon [5, 14, 20–22] (Fig. 12.1). However, it has also been argued that the survival advantage associated with lack of residual tumor has more to do with the biologic characteristics of the tumor itself than the skills of the surgeon involved [23–25]. This argument has led to a split in the approaches to EOC surgery, from a modest approach [26] with neoadjuvant chemotherapy followed by surgery [27] to a more radical approach, such as diaphragmatic surgery, liver resection, splenectomy, and partial pancreatectomy [28–30]. Although neoadjuvant chemotherapy can be considered in cases where optimal cytoreductive surgery is deemed unfeasible, it should not be considered to compensate for inadequate surgery [20, 27].

du Bois et al. [31] indicated that surgical outcome depends more on factors related to the surgeon and hospital than with the metastatic pattern of the tumor. Bristow et al. [32] reported on 1894 primary operations in patients with EOC, performed by 352 surgeons at 43 hospitals in the USA. After controlling for other factors, they found that surgery performed by a high-volume surgeon was associated with a 69 % reduction in the risk of hospital death, increased optimal cytoreductive surgery, shorter hospital stays, and lower costs of care. A review by Giede et al. [33] found that, in patients with advanced EOC, morbidity and mortality was associated with the specialty of the surgeon performing the operation. Patients who underwent surgery performed by gynecologic oncologists had a longer hospital stay, more blood loss, and longer operation time. On the other hand, these patients also had a lower perioperative mortality (2.4 % compared with 9.5 % for patients who had surgeons with other specialties, $p = 0.02$) [33, 34]. In a critical article, Covens [23] reported that cytoreductive surgery extent correlated with surgical morbidity.

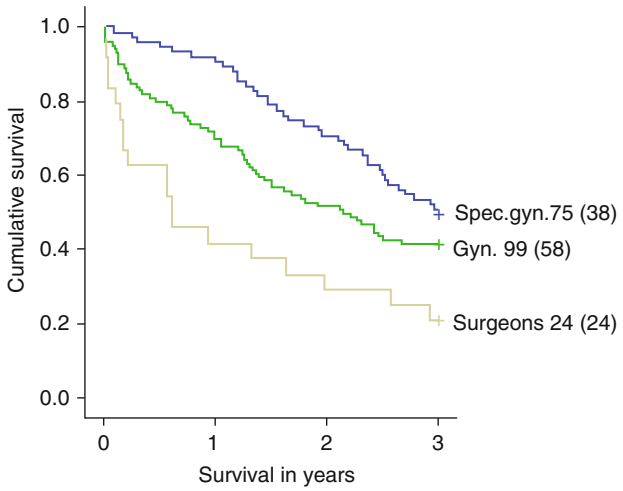

Fig. 12.1 Kaplan–Meier survival curves for advanced ovarian/peritoneal/tubal cancer (EOC) by specialty of surgeons performing initial surgery. Log-rank test, $p < 0.001$. Specialist gynecologist, number of patients treated 75, (38 patients are dead at end of follow-up). Gynecologist, number of patients treated 99 (58 patients are dead at end of follow-up). Surgeons, number of patients treated 24, (19 patients are dead at end of follow-up) (From Paulsen et al. [5] with permission)

Chemotherapy is given 10–15 % more often in specialized centers. Earle et al. [35] showed that patients with EOC were more likely to receive postoperative chemotherapy if their surgery was performed by a gynecologic oncologist (79 %) or general gynecologist (76 %) than by a general surgeon (62 %) ($p < 0.001$). In the review by Vernooij et al., the pooled relative risk for receiving chemotherapy was 1.14 (95 % confidence interval [CI] 1.07–1.22) for patients treated by gynecologic oncologists compared to those treated by general gynecologists [8]. Paulsen et al. [5] found that the odds ratios (OR) of receiving at least six courses of chemotherapy were 34 % lower for patients treated by general gynecologists compared to those treated by gynecologic oncologists (Table 12.1). Although differences in the administration of chemotherapy did not lead to differences in the survival of patients treated by gynecologic oncologists, they did influence the effect of hospital type on survival [8].

The majority of patients with advanced EOC in Europe do not receive care in specialized centers [1, 8, 31, 34]. The proportion of patients with advanced EOC who undergo surgical treatment at specialized hospitals varies substantially between European countries [1, 8, 31, 34]. For this reason we have performed an overview of patterns of surgery for advanced EOC, defined as FIGO stages III–IV, based on population-based studies from different European countries to try to illustrate these differences and explain the reasons behind them.

Table 12.1 Percentages of patients with advanced epithelial ovarian cancer who received platinum chemotherapy in specialized and general hospitals

First author [reference]	Stage of disease	Specialized hospital, % (*n*)	General hospital, % (*n*)	Odds ratio (95 % CI)
Tingulstad [36]	III–IV	100 (22)	85 (35)	1.63 (0.10–26.44)
Paulsen [5]	IIIc	99 (104)	98 (64)	8.24 (0.44–153.46)

Modification from Vernooij et al. [8]
CI confidence interval

Population-Based Studies in Europe

Effect of Hospital Type

An overview by Verleye et al. [1] showed that the proportion of patients with advanced EOC who undergo surgery at specialized hospitals varied substantially, from 18.0 % in the Netherlands to 92 % in health region IV in Norway (Trondheim) (Table 12.2). Most reports show that patients who undergo surgery in specialized hospitals (teaching, university, and high-volume hospitals) receive optimal cytoreduction more often than patients who undergo surgery in nonspecialized hospitals [8]. In a prospective population-based observational study from Norway by Paulsen et al. [5], optimal cytoreduction (no residual tumor) was achieved in 30 % of patients with stage IIIc EOC who underwent surgical treatment at teaching hospitals (TH) compared to 17 % at non-teaching hospitals (NTH) ($p<0.001$).

In a review of 19 articles, Vernooij et al. reported that the OR of achieving optimal cytoreduction in specialized hospitals varied between 1.9 and 6.0 [8]. They also reported that staging procedures were performed considerably more often in high-volume hospitals and in TH.

Effect of Specialized Surgeons

Aune et al. [44], Goff et al. [46], and Marth et al. [47] found correct staging procedures to be performed more adequately by gynecologic oncologists.

In a recent study, Engelen et al. [24] described a retrospective population-based observational study of 680 patients in the northern Netherlands between 1954 and 1997, in which optimal cytoreduction was achieved considerably more often by gynecologic oncologists than general gynecologists (24 % versus 12 %, $p=0.001$). The prospective population-based study from Norway reported that 23.7 % of patients with stage IIIc EOC achieved 0 cm residual tumor when surgery was performed by gynecologic oncologists. Tingulstad et al. [36] demonstrated that gynecologic oncologists achieved residual tumor <1 cm substantially more than general gynecologists (48 % versus 24 %, $p=0.04$). Junor et al. [22] showed a favorable trend of gynecologic oncologists to achieve residual tumor <2 cm compared to general gynecologists (36 % versus 28.7 %, $p=0.07$). European population-based studies are summarized in Table 12.3 and show the number of patients with

Table 12.2 Characteristics of population-based studies of surgical treatment of advanced epithelial ovarian cancer in specialized hospitals

Year of publication	First author [reference]	Country	Data collection	Time period	Study design	Number of patients operated in specialized hospitals (%)	Definition of specialized hospital
1997	Wolfe [37]	UK (South East England)	Regional cancer registry	1991	P	31/118 (26.2)	Teaching hospital
2000	Stockton [38]	UK (East England)	Regional cancer registry	1989–1993	R	475/989 (48)	Presence of radiotherapy and oncology
2003	Münstedt [39]	Germany (Hesse)	Regional quality assume project	1997–2001	R	532/824 (64.5)	Teaching hospital Tertiary care hospital
2006	Shylasree [40]	UK (Wales)	Regional audit project	1999	R	126/287 (44)	Teaching hospital
2006	Paulsen [5]	Norway	National cancer registry	2002	P	108/198 (54.5)	Teaching hospital
2006	Engelen [24]	The Netherlands (Northern region)	Regional database	1994–997	R	119/312 (38.2)	Teaching hospital
2006	Kumpulainen [41]	Finland	National cancer registry	1999	P	51 %	Teaching hospital
2006	Weide [42]	Germany (Northern region)	Hospital and general practitioner files	1995–2003	R	49/138 (35.5)	Teaching hospital
2007	Skírnisdóttir [43]	Sweden	Regional data base	1975–1993	R	137/517 (26.5 %)	Teaching hospital
2008	Vernooij [8]	The Netherlands	National cancer registry	1996–2003	R	1,557/8,621 (18)	Regional center with gynecologic oncologist
2011	Aune [44]	Norway Health region IV (Trondheim)	Regional cancer registry	2000–2005	R	247/269 (91.8)	Teaching hospital
2011	Fagö-Olsen [45]	Denmark	National cancer registry	2005–2008	R	1,433/2,025 (70.8)	Teaching hospital

Modified from Verleye et al. [1]
P prospective study, *R* retrospective study

Table 12.3 Details of population-based studies of advanced epithelial ovarian cancer; surgery performed by gynecologic oncologists

Year of publication	First author [reference]	Country	Data collection	Time period	Study design	Number of patients with surgery performed by a gynecologic oncologist (%)	Definition of gynecologic oncologist
1999	Junor [22]	UK (Scotland)	Regional cancer registry	1987, 1992–1994	R	351/1,866 (18.9)	Defined by committee
2005	Soegaard [48]	Denmark (North Jutland/Aarhus)	Aarhus hospital database	1999–2002	R	95.5 %	Not specified
2006	Kumpulainen [41]	Finland	National cancer registry (88 %)	1999	P	124/307 (40.3)	2-year training at university hospital
2006	Bailey [49]	UK (South West England)	Regional database	1998	P	252/361 (70)	Not specified
2006	Engelen [24]	The Netherlands (Northern region)	Regional database	1994–1997	R	184/512 (35.3)	Not specified
2006	Paulsen [5]	Norway	National cancer registry	2002	P	75/198 (37.8)	>1-year training at NRH[a]
2006	Shylasree [40]	Wales	Regional database	1997–1998	R	32/250 (12.8)	Not specified
2007	Skírnisdóttir [43]	Sweden (Örebro)	Regional database	1975–1993	R	137/447 (30.6)	Not specified
2011	Aune [44]	Norway (Trondheim)	Regional database	2000–2005	R	234/279 (83.8)	Not specified
2011	Fagö-Olsen [45]	Denmark	National cancer registry	2005–2008	R	855/1,160 (73.7)	Not specified

Modified from Verleye et al. [1]
[a]*NRH* Norwegian Radium Hospital, *P* prospective study, *R* retrospective study

Table 12.4 Details of population-based studies of advanced epithelial ovarian cancer treatment: surgical outcome

First author	Year	Country	Data source[a]	Time period	FIGO stage	% optimal cytoreduction (definition)
Junor [22]	1999	UK (Scotland)	Regional cancer registry	1987 and 1992–1994	III	27.3 % (≤2 cm)
Petignat [50]	2000	Switzerland (Valais)	Regional cancer registry	1989–1995	III–IV	42 % (≤2 cm)
Tingulstad [36]	2003	Norway (Trondheim)	Regional cancer registry	2000–2005	III–IV	48 % (<1 cm)
du Bois [51]	2005	Germany	Voluntary national QA program (48 %)	2001	IIb–IV	61.4 % (≤1 cm)
Soegaard [48]	2005	Denmark (North Jutland)	Central hospital database[b]	1999–2002	IIIc–IV	78.2 % (≤1 cm)
Kumpulainen [41]	2006	Finland	Voluntary national survey (88 %)	1999	III	47 % (0 cm)
Vergote [52]	2006	Belgium (Flanders)	Voluntary regional survey (45 %)	1998–2002	III	81 % (≤1 cm)
Engelen [24]	2006	The Netherlands (Northern region)	Regional cancer registry	1994–1997	III	62 % (≤2 cm)
Paulsen [5]	2006	Norway	National cancer registry	2002	IIIc	23.7 % (0 cm)
Marx [53]	2007	Denmark	National cancer registry	2002–2003	III	39 % (≤1 cm)
Weide [42]	2007	Germany (Northern Rheinland-Pfalz)	Patient files hospitals and general practitioners	1995–2003	III	37.8 % (≤1 cm)
Skírnisdóttir [43]	2007	Sweden (Örebro)	Regional cancer registry	1975–1993	III–IV	27 % (≤2 cm)
Marth [47]	2009	Austria	Voluntary national QA program (40 %)	1999–2004	I–IV	60.3 % (≤1 cm)
Akeson [54]	2009	Sweden (Western region)	Regional cancer registry	1993–1998	I–IV	58.6 % (≤2 cm)

Modified from Verleye et al. [1]
[a]For voluntary registration, the percentage of patients included is indicated between ()
[b]Surgery for ovarian cancer is centralized in one university hospital in the region, effectively covering 95.5 % of the cases during the reported period

advanced EOC who underwent surgery performed by a gynecologic oncologist in different European countries. It varies from 13 % in Wales [40] to 84 % in health region IV in Norway (Trondheim) [36]. Table 12.4 shows the surgical outcome (% optimal cytoreduction) from population-based studies of advanced EOC. Paulsen et al. [5] demonstrated that high-volume surgeons (more than ten patients with stage IIIc EOC per year) achieved a better short-term survival compared to low-volume surgeons (less than ten patients per year) (Fig. 12.2).

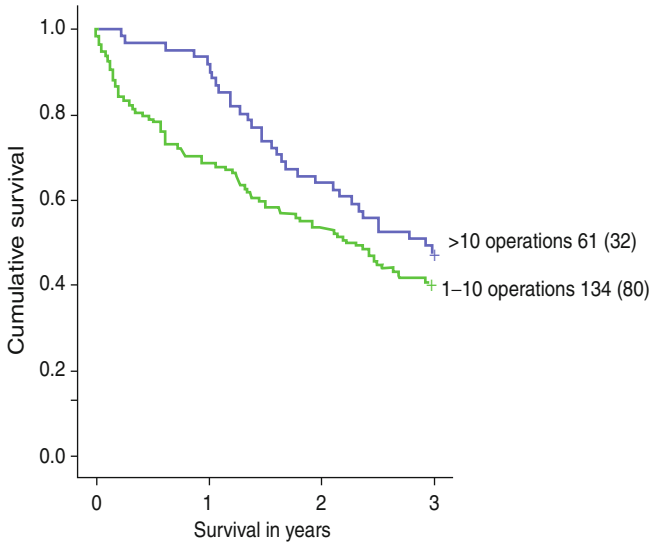

Fig. 12.2 Kaplan–Meier survival curves for advanced ovarian/peritoneal/tubal cancer (EOC) by number of operations per surgeons performing initial surgery. Log-rank test, $p=0.1$. Group with >10 operations, number of patients treated 61 (32 patients are dead at end of follow-up). Group with 1–10 operations, number of patients treated 134 (80 patients are dead at end of follow-up) (From Paulsen et al. [5] with permission)

Effect of Hospital Surgical Volume

Bristow et al. [55] reported that a number of population-based studies have demonstrated that specialized (gynecologic oncologists) and multidisciplinary care provided to patients with EOC by high-volume surgeons and high-volume centers was superior when compared to low-volume providers in the USA. A hospital surgical volume of 21 or more EOC cases per year was associated with a higher likelihood of receiving standard surgical treatment followed by adjuvant chemotherapy and was a significant predictor of improved survival. In Finland hospital surgical volume was associated with residual tumor size ($p=0.03$). When hospital surgical volume increased by ten patients per year, the OR for lack of residual tumor was 1.203 (95 % CI 1.02–1.42) [56]. However, other population-based studies have reported contradictory findings [57, 58]. Elit et al. [59] found that the effect of surgeons' specialty could not be explained by the surgical volume of hospitals in Canada. Only Schrag et al. [57] in the USA investigated whether the beneficial effects of high-volume hospitals were due to the presence of high-volume surgeons or to other factors. In their Cox model there was a significant association between hospital surgical volume and overall survival. However, when surgeon volume was included, the hazard ratio (HR) p-value of hospital type increased from 0.03 to 0.15. The proportion of patients with advanced EOC operated in high-volume hospitals (defined as ≥20 surgeries per year) varies between 25 % in Finland and 50 % in Tyrol, Austria [25, 47, 60, 61].

Effect of Surgeons' Specialty on Survival

The effect of surgeons' specialty on the survival of patients with advanced EOC with optimal cytoreduction is shown in Table 12.5. Up to now only five prospective studies have been published [5, 20, 37, 63]. Kumpulainen et al. [56] found that the strongest prognostic factor for cancer-specific survival was lack of residual tumor ($p<0.001$) and primary chemotherapy ($p<0.001$). In addition, there was a statistically significant association between cancer-specific survival and hospital surgical volume as a continuous variable ($p=0.04$). The 5-year survival differences between university hospitals and other hospitals were not statistically significant (45 months for both, $p=0.2$). Paulsen et al. [5] described the impact of hospital level and surgical skill on the short-term survival of 198 patients who underwent surgery in 2002 for stage IIIc EOC, tubal, and peritoneal cancer in a prospective population-based study in Norway. The data were derived from notifications to the Norwegian Cancer Registry and from medical, surgical, and histopathological records. The hospitals were grouped into TH and NTH, and the surgeons were classified according to specialty (gynecologic oncologists, general gynecologists, and general surgeons). The follow-up period was from 455 to 820 days. Short-term survival at 450 days was 79 % for women who underwent surgery at TH and 62 % for those who underwent surgery at NTH ($p=0.02$). However, after simultaneous adjustment for seven prognostic factors and residual tumor, the risk of death within 600 days after surgery at NTH was unchanged compared to TH, hazard ratio (HR 1.83). Women who underwent surgery performed by gynecologic oncologists compared to general gynecologists had a 20 % increased short-term survival ($p<0.0001$). TH and gynecologic oncologists achieved better short-term survival of patients operated for advanced EOC, tubal, and peritoneal cancer.

In 2011, Szczesny et al. [62] presented 8-year survival data at a conference in Milan, Italy. These are the only long-term results from a prospective population-based study that have been published to date. Eight-year survival was 15 % for women who underwent surgery at TH and 10 % at NTH ($p<0.05$), the median survival was 35.6 months at TH and 28.4 months at NTH ($p<0.05$). After simultaneous adjustment for four prognostic factors (age, histology, grade of differentiation, and residual disease), the risk of death within 8 years at NTH was unchanged (HR 1.38; 95 % CI 1.00–1.89) compared to TH. Junor et al. [22] found a decreased HR of death (0.78 $p=0.02$) for patients who underwent surgery performed by gynecologic oncologists even after adjustment for degree of cytoreduction and chemotherapy. In the case–control study by Tingulstad et al. [36], the median survival of patients who underwent surgery performed by gynecologic oncologists was 21 months compared to 12 months for patients whose surgery was performed by general gynecologists ($p=0.001$); 5-year survival was 42 and 37 %,

Table 12.5 Effect of surgeon's specialty on survival outcome in epithelial ovarian cancer

			Survival outcome				
First author [reference]	Surgeon	Stage of disease	Hazard ratio (95 % CI)	Median (months)	*p*-value	5 years survival %	*p*-value
Fagö-Olsen [45]	Gynecologic oncologist	III–IV	0.83 (0.70–0.98)	20	0.021	–	
	Gynecologist		1.00	16		–	
Kumpulainen [56]	Gynecologic oncologist	I–IV	1.00 (0.75–2.03)	–	0.4	45	NS
	Gynecologist		1.24	–		45	
Engelen [24]	Gynecologist	III	1.00	–		40	0.05
	Gynecologic oncologist		0.71 (0.54–0.94)	–		46	
Paulsen [5], Szczesny [62]	Gynecologic oncologist	IIIc	1.00	35.6	0.03	24[a]	0.05
	Gynecologist		2.11 (1.13–3.95)	23.4		17	
	General surgeon		3.08 (1.26–7.52)	7		–	
Tingulstad [36]	Gynecologic oncologist	III–IV	1.00 (3.0–29.5)	21	0.01	42	0.06
	Gynecologist		6.5	12		37	
Carney [63]	Other	I–IV	–	16	0.0012	–	
	Gynecologic oncologist		–	26		–	
Junor [22]	Gynecologist	III	1.00	13	<0.005	78[b]	NS
	General surgeon		1.32 (1.07–1.63)	–		78	
	Gynecologic oncologist		0.75 (0.62–0.92)	18		78	
Woodman [64]	Gynecologist	I–IV	1.00	48	<0.01	53[b]	<0.01
	General surgeon		1.58 (1.19–2.10)	7		20	
Skírnisdóttir [43]	Gynecologic oncologist	III–IV	1.03 (0.83–1.30)	19	NS	17	NS
	Gynecologist		1.00	21		19	
	General surgeon		1.25 (0.92–1.71)	13		9	

[a]From Szczesny et al. [62] 8-year survival
[b]3-year survival

respectively ($p=0.06$). Junor et al. [22] reported corresponding figures of 18 and 13 months ($p<0.005$). Both Tingulstad et al. [36] and Junor et al. [22] concluded that the improved survival of patients whose surgery was performed by gynecologic oncologists was due to the higher rates of cytoreduction achieved by this group.

Engelen et al. [24] found that the median survival of patients with advanced EOC whose surgery was performed by a gynecologic oncologist was 8 months longer than patients whose surgery was performed by a general gynecologist. The HR for patients whose surgery was performed by a gynecologic oncologist was 0.71 (95 % CI 0.84–0.94) compared with surgeries done by general gynecologists. Both Engelen et al. and Junor et al. found that the survival advantage of patients whose surgery was performed by a gynecologic oncologist was no longer significant when all stages of disease (stages I–IV) were analyzed together. They concluded that there was an effect of surgeon's specialty (in this case gynecologic oncologists) on survival in advanced EOC and in older patients, but not in the stages I–II and younger patients [22, 24].

Carney et al. [63] found that women who were older than 70 years and who underwent surgery performed by a gynecologic oncologist had a significant difference in median survival time compared to those whose surgery was performed by a general gynecologist (15 months versus 8 months). This is contrary to Elit et al. [59], who found no difference in adjusted HRs in a large cohort of patients over 65 years of age in the USA. This probably reflects the more complex nature of surgical treatment in advanced EOC, which requires better skills from the surgeons involved.

Discussion

In 1994, the National Institutes of Health in the USA convened a 14-member panel of experts in the management of ovarian cancer to generate a consensus statement of recommendations. The panel concluded that "Adequate and complete surgical intervention is mandatory primary therapy for ovarian cancer, permitting precise staging, accurate diagnosis, and optimal cytoreduction. The procedure is best conducted by a qualified gynecologic oncologist when there is a high probability of ovarian cancer…all women with suspected ovarian cancer should be offered a preoperative consultation with a gynecologic oncologist [65]."

During the past decade, compelling published work has accumulated to lend support to these consensus recommendations. These show that initial surgery for EOC is most appropriately performed by a gynecologic oncologist, preferably in centers with expertise in the multidisciplinary management of this disease [66]. Several population-based

studies have shown that the survival of patients with advanced EOC improved when they were treated either by a gynecologic oncologist or at a specialized high-volume hospital (Tables 12.3, 12.4, and 12.5). In Norway, centralization of patients with EOC stage IIIc to TH, compared to NTH, contributed to a considerably better 8-year survival [62, 67]. In contrast with expert opinion, the population-based studies summarized in this chapter show that optimal care (i.e., compliance with guidelines) is achieved only in a minority of patients in Europe and the USA [68].

Verleye et al. [1], Vernooij et al. [8], and du Bois et al. [31] discussed several possibilities in their review articles to explain why surgical treatment of patients with advanced EOC was so varied in Europe. The Key Sites study by the Northern and Yorkshire Cancer Registry and Information Service [69] showed no benefit of having surgery performed by a gynecologic oncologist compared with a general gynecologist after 5 years; indeed, the raw data suggested the contrary [70]. This is in contrast to the article by Junor et al. [22], which was the first population-based study to show that women with stage III EOC were more likely to survive 5 years when surgery was performed by a gynecologic oncologist compared with a general gynecologist or general surgeon. Despite the fact that the majority of the studies are in favor of the centralization of EOC services, the abovementioned controversies may be the reason why many general gynecologists are reluctant to refer patients with suspected advanced EOC to gynecologic oncologists, out of fear that the risks and the morbidity that radical cytoreductive surgery entail may outweigh the benefits for these patients. Therefore, complete centralization of advanced EOC services is precluded because of the inherent diagnostic difficulties the disease presents [70]. In addition, patients with advanced EOC, with low performance status and presenting with acute intestinal obstruction, are generally too ill to be referred to a tertiary center [70].

Critics of centralization claim that no randomized controlled trial has been undertaken, and it is true that to-date attempts to perform randomized studies reviewing the relationship between initial cytoreductive surgery and survival in patients with advanced EOC have been unsuccessful [1, 70]. Although ideally the effect of treatment settings on outcomes should be investigated in a randomized controlled trial, the nature of EOC and its often complex treatment make this impossible and may even be considered inappropriate as all studies reviewed represent level IIb evidence. Well-designed cohort studies and large prospective population-based observational studies may be of more value than poorly designed randomized studies [5, 71]. The surgical skill of general gynecologists may also play a role in treatment outcomes. Indeed, many have not been trained in advanced EOC cytoreductive surgery (bowel resection, diaphragmatic surgery, pelvic, and paraaortic lymphadenectomy, splenectomy, liver resection, and peritonectomy), despite the existence of training programs and certification in both Europe (the European Society of Gynecological Oncology) and the USA (adherence with National Comprehensive Cancer Network [NCCN]) [72, 73].

Nothing has changed when it comes to the referral of patients with advanced EOC to tertiary centers in most European countries. However, in Scandinavia important changes have been established. The publication of Paulsen et al. [5] showing that survival was considerably longer among patients treated at TH compared to NTH sparked a large debate in the Norwegian media. The health minister took part in the debate and decided in 2006 that all patients with advanced EOC should be referred to the four TH in Norway. Before her decision, these patients underwent surgical treatment in 38 different hospitals in Norway. In the beginning some general gynecologists were not satisfied because they did not believe that the survival benefit was significant enough. They also found it inappropriate to deny a patient a timely operation by a local general gynecologist with the relevant skills when there was a delay in the specialized center. They also claimed that long journeys and isolation from family and friends were not good for the patients and that centralization could lead to a loss of skills among general gynecologists in the surgical treatment of EOC, particularly regarding staging procedures. At the time of Paulsen's publication [5], only 55 % of the patients with advanced EOC underwent surgical treatment at a TH. Today the figure is about 90 %, the same as Tingulstad et al. [36] showed for health region IV in Norway. General gynecologists in all health regions of Norway are now loyal to the decision of the health minister.

In Denmark primary operations to treat EOC were performed in 47 departments in 2003 including treatment of stage III in 32 departments [45]. Denmark has the highest mortality of EOC compared to other Nordic countries [74]. In spite of the introduction of cisplatin and paclitaxel-based chemotherapy, the mortality rate has not declined since the mid 1970s [74]. In the observational nationwide study by Fagö-Olsen et al., patients with stages III–IV EOC benefited from treatment in a specialized referral center [45]. Since 2005 the number of departments involved in the primary surgical treatment of EOC has declined significantly, from 47 to 6 institutions, and the organization of surgical treatment for advanced EOC and 5-year survival has improved since the Danish health board recommended in 2001 that surgery be performed at five high-volume hospitals (defined as treating >100 patients/year) [75].

Apart from residual tumor, another major issue that may influence patient survival is treatment according to prevailing guidelines. Guidelines for the treatment of EOC have been published by regional, national, and international organizations [24]. In Western Sweden, Akeson et al. reported on

the effect of the 1993 introduction of clinical guidelines, after which the 5-year survival rate improved compared to that during the preceding period and compared to the rest of Sweden [8, 54].

We observed greater compliance with surgical guidelines among gynecologic oncologists than general gynecologists. Thus, treatment by a gynecologic oncologist in a specialized center is a key element for a positive outcome. Other factors in the setting, like chemotherapy, also help to explain the better results obtained in specialized hospitals [5, 62]. Engelen et al. [24] reported a 5-year survival of 32 % among patients with stage III EOC when guidelines were followed and 11 % when they were not (HR 1.97; 95 % CI 1.45–2.68).

The mere existence of guidelines does not guarantee their application. At the 2011 ASCO meeting in Chicago, Powell et al. [68] presented a project from the Society of Gynecologic Oncology on whether adherence with NCCN was associated with improved survival in 144,449 patients from the National Cancer Data Base. Their objective was to assess the influence of adhering to NCCN guidelines on 5-year survival and the frequency of adherent care from 1998 to 2007; 96, 802 patients were eligible. Overall only 42 % of these women appeared to receive care that was adherent to guidelines. Of the 22,552 patients reported to have undergone surgical treatment alone, only 8 % received adherent care. 49,160 patients had mature survival data, and a multilevel survival analysis showed significantly decreased survival for patients receiving non-adherent care (HR 1.44). Powell et al. concluded that compliance with NCCN guidelines is associated with improved survival and quality of care. "Unfortunately non-adherent care is common in our health system, and appears to diminish survival [68]."

One may ask: Is there a role for general gynecologists in the management of ovarian cancer? Undoubtedly a general gynecologist may retain or develop the necessary surgical skills to operate on women with EOC. We think that general gynecologists will continue to have an important role in the diagnosis and referral of patients with suspected EOC. In addition, general gynecologists who perform intra-abdominal surgery will need to develop guidelines agreed with the specialized center to deal with undiagnosed EOC [54, 76]. The studies by Kumpulainen et al. [60] illustrated that specialty surgical training is not the only marker of surgical experience and that in regions without trained gynecologic oncologists, increased hospital surgical volume and centralization of care can also lead to improved patient outcomes. The findings by Kumpulainen et al. have led to the centralization of EOC care in Finland [60]. Nevertheless, even after prognostic variables such as those described above are taken into account, there remains a residual survival benefit when patients are referred to a multidisciplinary team, an "oncology team," or to gynecologic oncologists. Only larger units will have size-specific medical oncologists, histopathologists, and radiotherapists to develop expertise in diagnosis and management of EOC. In addition, academic links and participation in national and international trials are more likely in a large well-organized multidisciplinary group [76].

A pilot project to investigate patients' self-reported experiences of the centralized gynecologic cancer service and evaluate women's experience in terms of information, psychological distress, and worry after treatment for EOC has been published by Hackman et al. and Olaitan et al. [77, 78]. The vast majority (97 %) of responders indicated a preference to attend the centralized clinic. Overall women rated travel, isolation from family, and cost as unimportant. Extremely high overall levels of satisfaction reflected the women's positive experience at the centralized clinic [77]. As a matter of fact, the study showed that the majority of the responding women wanted to be treated and receive follow-up at the centralized clinic [77, 79].

Conclusion

Prospective population-based studies (Level IIb) from England [20], Finland [56], and Norway [5, 62] have shown substantially better survival for patients treated at TH compared with NTH. Optimal treatment of patients with advanced EOC consists of aggressive upfront surgical treatment and chemotherapy. However, in this chapter we have shown that a substantial number of women with EOC in Europe (<50 %) do not receive optimal surgical treatment. To achieve this goal it has been advocated that patients be centralized to comprehensive cancer centers providing interdisciplinary collaboration.

Since EOC is a relatively rare tumor type, it should benefit from centralization to dedicated centers. However, it is important that the arguments give sufficient resources, infrastructures, and control to ensure that the centralization policy is working. This fact demands that national health care systems secure sufficient education and training of the involved medical staff.

Finally, we agree with Giede et al. [33] that:

1. Patients with advanced EOC who undergo surgery performed by gynecologic oncologists are more likely to receive optimal cytoreductive surgery (Level IIb).
2. Patients with advanced disease operated on by gynecologic oncologists have an improved median and overall 5-year survival (Level IIb).
3. Patients with advanced EOC who undergo surgery performed by general gynecologists can have survival equal to patients whose surgery is performed by gynecologic oncologists if rates of cytoreduction are equal (Level IIb).
4. Patients with early-stage EOC are more likely to have comprehensive staging when operated on by gynecologic oncologists, allowing for better selection of patients requiring adjuvant chemotherapy (Level IIb).

What Is the Best Model for Gynecologic Cancer Services: Does Centralization Help? Arguments Against Centralization

Craig Underhill and Ayesha Saqib

Non-ovarian Gynecologic Malignancies

Incidence rates and survival differ across the various gynecologic malignancies. Cancer of the cervix is the most common gynecologic cancer worldwide while cancer of the vulva and vagina are much less common. There have been reports of an "epidemic" of endometrial cancer due to rising rate of obesity.

The treatment for early cervical cancer is surgery and for advanced disease chemoradiotherapy. The effect of centralization on outcomes of patient with cervical and vulvar cancer has not been well reported in the literature. Importantly, Brookfield et al. [80] in their study showed no demonstrable benefit for either high-volume center or teaching status on patient overall survival for all five gynecologic malignancies.

Endometrial cancer is managed mainly with surgery. Centralization of endometrial cancer results in accurate staging; however, it is unclear whether this affects the outcome [81]. The surgical outcomes for early endometrial cancer are similar whether the procedure is performed by a general gynecologist or by a gynecologic oncologist [82].

Surgical Aspect of Gynecologic Cancer

Surgical interventions are required for gynecologic cancer for accurate staging and for optimal removal of the tumor. These interventions are sometimes undertaken by general surgeons, by general gynecologists, or by gynecologist oncologists depending upon availability. In rural/regional Australia general and other surgeons provide a substantial proportion of local oncology surgery especially in gynecology surgery (48 %) [83]. Although much literature has suggested that the patient is likely to have accurate staging of the disease if the surgical procedure has been undertaken by a gynecologist oncologist, there are no data to show a survival benefit from such interventions. For instance, in endometrial cancer optimal surgical staging including lymphadenectomy rates are high in patients operated upon by gynecologic oncologists; however, available data are unable to show any survival advantage from this approach and the exact role of this extended surgical staging is very controversial [80]. Complex procedures are more time consuming and need extensive expertise often involving multiple surgeons at the same operation. Morbidity rates can be high. Hoekstra et al. [82] found that for early endometrial cancer, the cost and operative time are increased when general gynecologists operate but perioperative outcomes were similar when compared to procedures performed completely by a gynecologic oncologist.

Multidisciplinary Care

Multidisciplinary management of gynecologic cancer seems to improve survival [84]. Crawford and Greenberg [85] reported an 8 % survival benefit with centralization and a multidisciplinary approach. Interestingly it is unclear whether this effect is purely due to centralized care or a multidisciplinary approach or both and as has been pointed out, stage migration from lower to higher stages in centralized units ensures better results for both well-staged lower stage cases and well-staged higher stage cases with microscopic spread. One can clearly argue that if multidisciplinary approach is available via networking rather than centralization, it may still be able to affect survival outcomes and the only variable really relates to surgical expertise.

Patient Views

Optimal cancer care is more than just surgery or delivery of anticancer treatment. It incorporates patient awareness, continuous support, and future planning. Evidence suggests that cancer survival rates are significantly lower in rural and regional areas than in major metropolitan centers [86]. Cancer service deficiencies in these areas are contributory to poorer outcomes [83]. The care needs for patient living in rural and regional areas are different and sometimes very unique [87, 88]. A centralized approach in a country like Australia often involves patients travelling long distances at great financial and emotional cost.

Alternatives to Centralization

The survival and economic benefits or otherwise of centralization are not clear [89]. The formation of networks offers more possibilities than centralization. The establishment of designated centers like Regional Cancer Centers of Excellence (RCCEs) in Australia which provided multidisciplinary care and improved support and educational services, with the formation of clinical partnerships with major metropolitan centers, is one way to overcome disparities in outcomes [90]. When some cancer services are provided locally, the uptake of treatment increases [91].

The Model

One possible non-centralized model is a "shared-care" or "hub and spoke" arrangement to maximize treatment outcomes and minimize patient inconvenience. Supported by technological advances in communication, such as teleconferences and web conferences, it is possible to construct such a networked model. For example, when a diagnosis is made, patients can be referred to a specialist unit for surgery. Once surgical management is completed, the patient's case can be discussed in a multidisciplinary meeting that includes regional service providers linked in via teleconference or web conference. Responsibility for components of care such as chemotherapy and radiotherapy care can be devolved to the regional providers using agreed protocols. In particular supportive care can be managed locally and primary care providers can be linked in to the multidisciplinary meeting as well. Follow-up care can be shared using agreed protocols. This model can include a component of mentoring to ensure support, up-skilling and continuing professional development of regional care providers. In addition recruitment to health services and clinical research protocols can be optimized. Thus, access to care according to best practice guidelines can be provided across the care continuum. This allows patients to receive safe care as close to home as possible. We have had some experience of demonstration projects in hematological malignancies and lung cancer [92, 93]. These have informed the development of a sustainable model in the management of gynecologic malignancies and sarcomas. Other health services projects have explored similar network development in other cancers [94].

Discussion

Gynecologic malignancies include five major types of cancers. Centralization may improve gynecologic cancer survival; however, evidence is lacking. Most of the available evidence is for ovarian cancer in developed countries and therefore lacks generalizability [38, 95]. The data on surgical outcomes and their importance are still controversial [59, 96, 97] and relate only to ovarian cancers. There are no studies available to determine the effect of centralization on quality of life nor for cost-effectiveness and comparison across different health systems. Available evidence is biased and randomized controlled trials are needed to determine whether it is the surgical intervention or alternatively patient- and disease-related factors that determine any improved survival in this group of women [79, 98–100]. Additional research is required to compare other health system models to centralization, to see the impact of centralization on quality of patient's life, and also health economic studies are required to further explore this area.

Concluding Comments

- Additional research is required to compare other health system models to centralization, to see the impact of centralization on survival and quality of life.
- Clinical networks allow the possibility to develop shared-care models to ensure patients receive the best possible and safe care as close to home as possible. This could include centralized surgical care but other components of care being delivered across a facilitated network.

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When Should Surgery Be Performed for the First-Line Treatment of Advanced Ovarian Cancer?

13

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Summary Points

- Minimal residual disease after surgery is associated with better outcomes.
- Predicting operability to achieve no or minimal residual disease is inexact.
- There are two randomized trials showing no survival difference in patients with very advanced disease given primary (neoadjuvant) chemotherapy as opposed to up-front primary surgery.
- Targeted agents and novel schedules such as intraperitoneal or dose-dense chemotherapy have not been evaluated in this context.

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The Case for Neoadjuvant (Primary) Chemotherapy

Introduction

Surgery, with the aim of achieving maximal tumor debulking, in combination with platinum-based chemotherapy, is the cornerstone of first-line treatment for ovarian cancer. Unusually among other solid tumors and despite a lack of evidence from randomized controlled trials, it is clear that cytoreductive surgery has an important therapeutic role for even advanced disease (FIGO stages III and IV). The aim of surgery is also clear: it is to remove all visible disease. The timing of surgery, however, is a current area of controversy.

We argue the case for neoadjuvant chemotherapy with delayed primary debulking surgery. This approach has been shown to be equivalent in terms of survival to immediate surgery followed by chemotherapy in the EORTC 55971-NCIC trial with less postoperative mortality and morbidity [1]. There are areas of controversy in the interpretation of this study but we also argue that neoadjuvant chemotherapy provides additional benefits in providing opportunities for translational research and in the development of personalized medicine.

What Is the Role of Primary Cytoreductive Surgery in Advanced Ovarian Cancer?

Women with ovarian cancer typically present with advanced disease, most commonly with abdominal peritoneal metastases following transcoelomic dissemination (FIGO stage III) and more rarely with visceral metastases or disease outside the abdomen (FIGO stage IV). Debulking surgery followed by chemotherapy has been standard treatment for these women since the observation by Griffiths in 1975 that in a series of patients undergoing surgery for advanced disease, those with residual tumor nodules <1.5 cm in maximum diameter lived longer than those with residual >1.5 cm [2]. Historically, surgery was performed with the aim of accurate

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staging, obtaining tissue for histological diagnosis, and debulking the volume of intra-abdominal disease [3]. With advances in imaging and invasive radiology, its role now is essentially cytoreductive.

However, this is unique among solid tumors, where such surgery generally has no impact on survival and the management of patients with widely disseminated disease is primarily by palliative chemotherapy. A number of explanatory hypotheses have been put forward including that debulking of large tumor masses enhances the efficacy of chemotherapy by removal of poorly vascularized areas, resistant clones and tumor stem cells, and through a reduction in the total number of cancer cells [4]. However, none of these theories have been directly proven to apply [5] and, with the development of highly effective platinum-taxane combination regimens with response rates of >75 %, the relevance of arguments dictating that surgery should be performed prior to chemotherapy is now questionable.

Despite this, there is compelling evidence that surgery has an important therapeutic role. This is mainly based on the observation from multiple retrospective series, analyses of clinical trial data, and meta-analyses that completeness of cytoreduction is an important prognostic factor for improved survival [2, 3, 6–10]. Early studies suggested that tumors debulked to <1 cm maximum residuum had a more favorable prognosis, but, more recently, the target for "optimal debulking" has been revised downwards to no visible residual disease [11]. In the ICON5/GOG-182 trial, median survival of the cohort of patients entered with 0 cm residual disease was 68 months, compared to 40 months for those with 0.1–1.0 cm and 33 months for those with >1 cm residual disease [12].

Although consistent across multiple studies, this evidence is inherently limited by its observational nature. There is discordance between studies about the relative prognostic importance of debulking compared to other factors. While some have suggested that optimal debulking can mitigate the adverse effect of more advanced stage [7], others have found that the survival benefit is less in more advanced disease in terms of stage [13] or initial tumor volume [14]. Without a randomized trial directly comparing debulking surgery with no surgery, it is not possible to say conclusively whether women whose tumors are optimally debulked have a better prognosis because of the outcome of their surgery or whether they have intrinsically biologically favorable disease, which determines not only prognosis but also the likelihood of optimal debulking.

However, while it is important to acknowledge these limitations, they do not mean that optimal surgery is not beneficial. Perhaps the best evidence for the role of surgery comes from an EORTC trial which investigated the efficacy of interval debulking surgery following suboptimal primary surgery. In this study, conducted between 1987 and 1993, 319 women with incompletely cytoreduced stage IIB–IV disease were randomly assigned to a second operation during cisplatin-cyclophosphamide chemotherapy or to no further surgery. Median survival was extended from 20 to 26 months, and there was a 10 % increase in 2-year survival, from 46 to 56 %. In addition, within the group undergoing interval surgery, median survival for those with tumor debulked to <1 cm residuum was 41.6 months compared to 19.4 months in those with >1 cm disease at the end of a second operation [15]. From these results it may be inferred that optimal surgery has a therapeutic (and not just prognostic) effect. However, it again challenges the optimum timing of surgery, suggesting that it may be delayed until after neoadjuvant chemotherapy and that this could be preferable by reducing the need for a second operation.

What Are the Arguments for (and Against) Neoadjuvant Chemotherapy Versus Primary Surgery?

Surgery for advanced ovarian cancer is complex and analyses from several countries with different health care systems confirm that operations performed by specialist gynecological oncologists are more likely to result in optimal debulking [16–18]. In some centers, the pursuit of maximal cytoreduction has led to the practice of ultraradical surgery, involving extensive resection of upper abdominal peritoneal disease, bowel surgery, and even resection of intrathoracic and visceral metastases. Retrospective series from selective specialist centers have reported impressive optimal debulking rates and improved survival with this strategy [19, 20], in the region of 67.5 % debulking to <1 cm, with 47 % 5-year survival for patients with stage IIIC disease [20], but current evidence is limited by a lack of randomized data [21] and these operations may be associated with significant morbidity.

Proponents of primary surgery argue that most tumors can be optimally debulked by a single up-front surgical procedure if performed by an appropriately trained surgeon and that only a small minority unfit for surgery or with the most extensively disseminated disease are not candidates for this approach [22]. However, population-level data from both the USA and Europe show this is not the experience of many women with ovarian cancer [23, 24]. In a recent analysis of US SEER and Medicare data, of 8,211 women diagnosed with stage III/IV ovarian cancer between 1995 and 2005, 58.8 % underwent primary surgery, 24.6 % received primary chemotherapy (32 % of whom subsequently underwent surgery), and 16.6 % received no active anticancer therapy [23]. It is therefore evident that for a significant number of women diagnosed with advanced ovarian cancer, primary surgery has not been a deliverable treatment. Without arguing against the need for improvements in standards of care and access to treatment in specialist centers, it is not realistic to advocate that most women should undergo complex, ultraradical

primary surgery, and, alternative active management strategies that result in more women undergoing a combination of optimal chemotherapy and surgery are needed.

The case for neoadjuvant chemotherapy is essentially that complete surgical cytoreduction is an important determinant of survival. While this may be achieved through primary surgery, a significant proportion of women will either (1) undergo up-front surgery with only suboptimal outcome; (2) suffer significant morbidity (or mortality), which may affect ability to deliver postoperative chemotherapy; or (3) be unable to undergo any surgery due to extent of disease or disease-related poor performance status.

The arguments for using neoadjuvant chemotherapy in preference to primary debulking surgery are the following:

1. Response rates to carboplatin-paclitaxel chemotherapy are high and the majority of patients treated experience a rapid symptomatic and radiological response, consequently:
   (a) Increasing the number able to undergo surgery
   (b) Increasing optimal debulking rates
   (c) Decreasing surgical morbidity by allowing maximal cytoreduction to be achieved with less extensive surgery
2. A single operation midway through chemotherapy will avoid a second interval debulking procedure in a proportion of patients who would have been suboptimally debulked with primary surgery.
3. Conversely, it allows early identification of those with platinum-refractory disease, whose prognosis is so poor that they would be unlikely to benefit from debulking surgery.

The main concerns cited against using neoadjuvant chemotherapy are the following:

1. Using chemotherapy prior to debulking may promote development of chemo-resistant clones [25].
2. There is a risk of inaccurate diagnosis.
3. Operating after there has been a response to chemotherapy permits an overly conservative surgical approach and may lower standards by allowing surgery to be performed by nonspecialist surgeons [22].
4. Improvement in symptom-control and quality of life may be slower.

There is an extensive body of observational studies reporting optimal debulking rates and survival from centers employing either primary debulking or neoadjuvant approaches to treatment of women with stage IIIC/IV ovarian cancer. Conflicting meta-analyses have been published showing evidence of poorer outcome with primary chemotherapy and increase in optimal debulking rates with equivalent survival, respectively [26, 27]. Comparison of these nonrandomized studies is limited as those reporting on primary chemotherapy tend to include patients with adverse prognostic factors. Assessment of the relative efficacy of the two approaches requires consideration of the EORTC 55971-NCIC trial, which randomized women who were considered eligible for resection either to primary debulking surgery or to neoadjuvant chemotherapy with interval surgery [1].

Key Evidence: The NCIC-EORTC 55971 Trial

This study was developed to investigate whether women with stage IIIC/IV ovarian cancer may undergo a single operation midway through primary chemotherapy rather than primary surgery followed by chemotherapy, without compromising survival. As the first randomized evidence for the timing of surgery in first-line treatment, it is key to determining whether neoadjuvant chemotherapy is an acceptable standard of care.

In the study, 670 women were randomly assigned to primary debulking surgery followed by six cycles of platinum-based chemotherapy or to receive chemotherapy with delayed surgery. Participants were recruited between 1998 and 2006 from 59 institutions in Belgium, the Netherlands, Norway, Italy, Spain, the UK, and Canada. To be eligible, women had to have histologically confirmed stage IIIC or IV epithelial ovarian, primary peritoneal, or fallopian tube cancer that was considered suitable for resection at diagnosis. Confirmation by cytology was permitted providing a pelvic mass with abdominal metastases >2 cm or stage IV disease was present, and GI cancer had been excluded. Stage IIIC was defined by the presence of intra-abdominal metastases, and patients with locoregional nodal disease only were not eligible. Surgical procedures were not specified but were required to be a maximal effort at cytoreduction performed by a specialist gynecological oncologist.

Median survival was 29 months in participants randomized to primary surgery and 30 months for those in the neoadjuvant arm, with no evidence of a detrimental effect for treatment with neoadjuvant chemotherapy (hazard ratio (HR) for death was 0.98 with 90 % confidence interval (CI) 0.84–1.13). Optimal debulking rates were notably higher in these women, with 53 % undergoing maximal cytoreduction to no visible residual disease compared to 19 % in the primary surgery group. There was remarkable variation between countries (6.3–62.9 % maximal cytoreduction in the primary surgery arm) but no significant association between country and survival was found, and differential selection bias has been proposed as an explanation. Completeness of cytoreduction was the strongest independent prognostic variable (ahead of stage, initial disease volume, histotype, and age). A number of post hoc subgroup analyses were performed, with the only notable finding being a suggestion that patients with smaller volume disease at randomization (<5 cm maximum tumor diameter) had improved survival with primary surgery rather than primary chemotherapy. Postoperative mortality and adverse events including infections, hemorrhage, fistulae, and venous complications were higher in the primary surgery group. Quality of life assessments were performed during treatment and follow-up, with no observable difference between treatment groups. Histological diagnosis after surgery differed from pre-randomization diagnosis in only 18 patients (11 assigned to primary surgery and 7 to neoadjuvant chemotherapy).

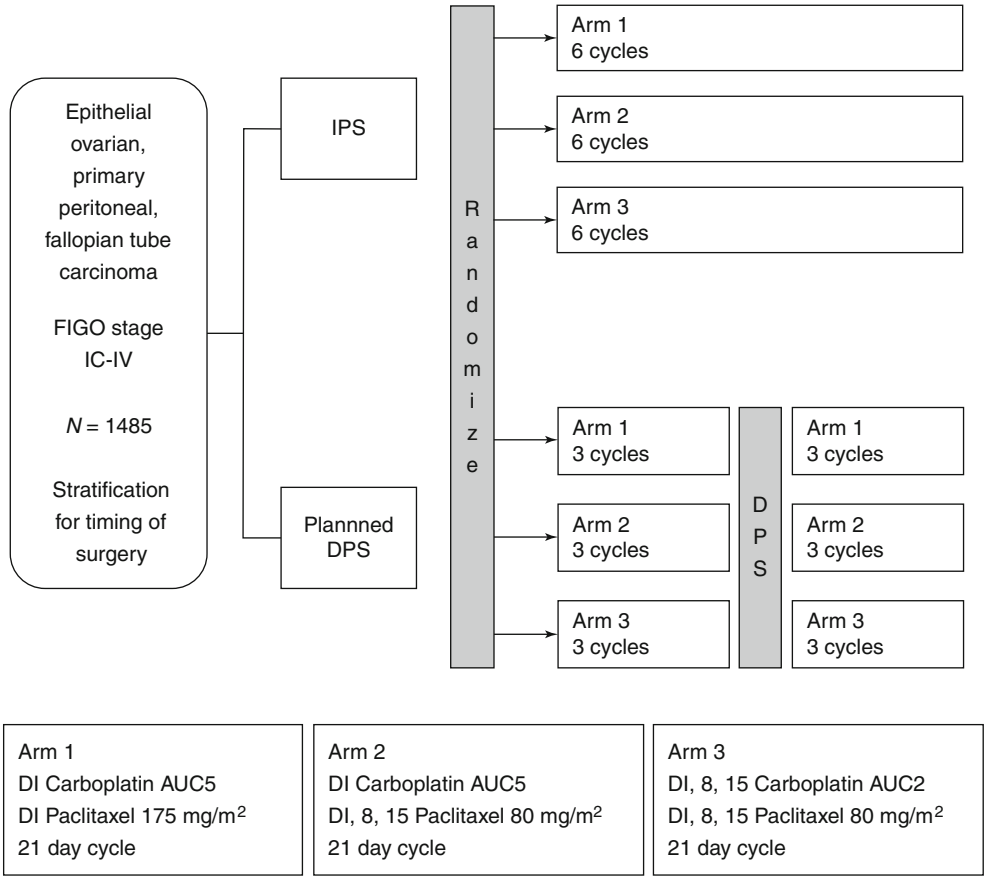

Fig. 13.1 ICON8 trial schema. *IPS* immediate primary surgery, *DPS* delayed primary surgery

An area of controversy in the interpretation of this study is the relatively poor survival compared to other contemporary trials [12, 28–30], and it has been hypothesized that survival in the primary surgery group in particular was adversely affected by low rates of optimal debulking. In addition, it is true that higher rates of optimal debulking following neoadjuvant chemotherapy did not lead to longer median survival in that group. It has been suggested that this may indicate the development of increased chemotherapy resistance with neoadjuvant chemotherapy. It is not possible to resolve these concerns conclusively but it is self-evident from the design of the trial and baseline characteristics that participants had worse prognosis disease than in other first-line trials, and survival is not comparable. Additional supporting evidence has now been provided by the MRC CHORUS trial, which recruited 552 women from the UK and New Zealand between 2004 and 2010, and had a similar design to the EORTC study [31]. In this trial, the women recruited had very advanced ovarian cancer: nearly 20 % had a WHO performance status of 2 and 25 % had FIGO stage IV disease. The median survival of participants randomized to neoadjuvant chemotherapy was 24.5 months compared to 22.8 months in the primary surgery arm and treatment with neoadjuvant chemotherapy was shown to be non-inferior to primary surgery (HR 0.87, 95% CI 0.71-1.05).

Decreased morbidity and mortality without detriment to survival or quality of life justifies primary chemotherapy as an acceptable standard of care for women with stage IIIC or IV disease. This is reflected in current consensus guidance [11] and it is being increasingly employed in routine clinical practice. A recent Danish registry study reported that 30 % of stage IIIC/IV patients now receive primary chemotherapy [32], and, anecdotally, this reflects our experience in the UK. It is important that clinical trials of new therapies in first-line treatment accommodate this pathway of care, as has been done with the current GCIG ICON8 trial (NCT01654146) (see Fig. 13.1). There are, however, justifiable concerns about generalizability to smaller volume or nodal stage III disease [33]. In addition, it should not be seen as an "easier" option [34, 35]. Treatment with primary chemotherapy requires high-quality care with accurate histological diagnosis prior to treatment, timely delivery of chemotherapy and surgery to maintain intensity, and specialist surgery.

How Should the Neoadjuvant (Primary Chemotherapy) Approach Be Developed?

Questions now should focus on refining the neoadjuvant approach, in particular, which patients should or should not

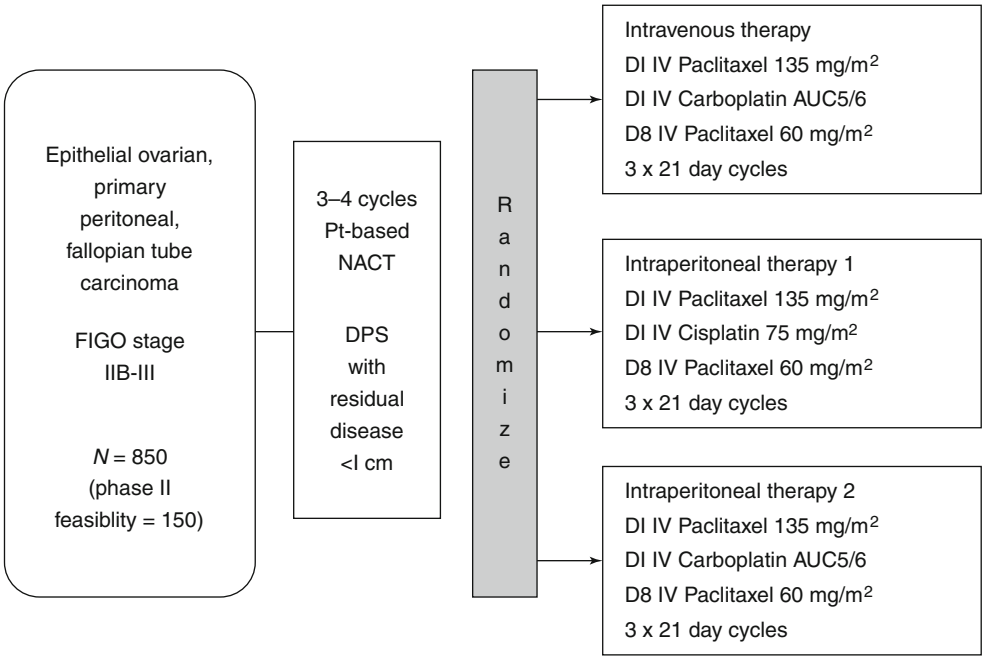

Fig. 13.2 PETROC trial schema. *NACT* neoadjuvant chemotherapy, *DPS* delayed primary surgery

be managed with neoadjuvant chemotherapy in preference to primary surgery, and can treatment regimens be optimized to improve survival?

1. Which patients should be offered neoadjuvant chemotherapy?

   How to select patients for neoadjuvant chemotherapy or primary debulking is a matter of ongoing debate [36]. It is becoming generally accepted that some women are at higher risk of morbidity from complex primary surgical procedures and that they may be more safely managed using neoadjuvant chemotherapy. Risk factors consistently identified are a combination of increasing age, poor performance and nutritional status, widely disseminated or stage IV disease, and complexity of surgery [37–39]. In women who might be considered suitable for an operation, there is evidence that for stage IV disease, neoadjuvant chemotherapy may result in prolonged survival and increased likelihood of maximal cytoreduction [40, 41].

   In general, women at high risk of postoperative complications, those with stage IV disease and those without realistic expectation of optimal debulking at primary surgery may be best treated with neoadjuvant chemotherapy. What is not clear is how to determine whether maximal cytoreduction is feasible. Despite multiple studies investigating the predictive value of imaging criteria and laparoscopy, a universally applicable model has not yet been developed [42].

2. Can we optimize pre- and postsurgery chemotherapy regimens?

   In the EORTC study, 88 % of women in the neoadjuvant group received carboplatin-paclitaxel and 85 % completed at least 6 cycles of chemotherapy. It is therefore clear that combination regimens may be utilized with delayed surgery. However, first-line systemic therapy is evolving with evidence that both dose-dense carboplatin-paclitaxel regimens and bevacizumab-containing regimens may result in prolongation of survival [28, 30, 43]. The safety and feasibility of combining dose-dense regimens and delayed surgery will be investigated in the ICON8 trial in which patients are treated either with standard three-weekly chemotherapy or a dose-dense schedule (see Fig. 13.1). In view of the toxicity profile of bevacizumab, care must be used when employing it in the perioperative setting, and while shown to be safe in breast, gastric, and colorectal cancer [44–48], the complexity of ovarian cancer surgery, particularly bowel resection, means that studies looking specifically at safety are required before its widespread adoption.

   An alternative approach may be to modify the postoperative regimen to counteract the possibility of developing chemoresistance or on the basis of observed response to neoadjuvant treatment. The first study to address this is the NCIC-CTG OV21/NCRI-PETROC trial (NCT00993655), which compares intraperitoneal and systemic platinum-taxane chemotherapy in women who have had optimal debulking surgery following conventional neoadjuvant treatment (see Fig. 13.2). The first stage, a randomized phase II feasibility study to compare two intraperitoneal experimental arms is underway and the intention is to continue with one of these in a larger study to compare efficacy with intravenous chemotherapy [49].

The Potential of Neoadjuvant Chemotherapy: Translational Research and Personalized Medicine

Perhaps the most exciting aspect of the increasing adoption of neoadjuvant chemotherapy is its potential for promoting translational research. This approach permits collection of pre- and post-chemotherapy exposure tumor tissue and blood and allows functional imaging studies to be performed, which could be used to identify early signals of platinum-taxane resistance and markers of response. A comprehensive sample collection should be included in clinical trials that incorporate neoadjuvant chemotherapy to allow these high-quality correlative studies to be undertaken. In the ICON8 trial sample collection (TRICON8), we will collect paired tumor tissue samples from all patients undergoing delayed surgery, which will be an invaluable resource for future research. The development of targeted therapies in combination with chemotherapy may also be enhanced through "window-of-opportunity" studies [50].

An ultimate goal of the neoadjuvant approach must be to facilitate personalization of treatment with adjustments to systemic therapy based on comprehensive assessment of an individual's markers of response and developing resistance to preoperative chemotherapy.

The Case for Primary Debulking Surgery

A number of facts are indisputable in relation to epithelial ovarian cancer:

- The majority of patients with this malignancy (75 %) present with stages III and IV disease.
- There is currently no good screening test available to help identify these patients early. Patients who are diagnosed and treated early, however, have a better prognosis [51].
- The standard management of patients presenting with ovarian cancer is up-front complete surgical debulking with the aim to reduce residual tumor volume to ≤1 cm and ideally to no macroscopic disease followed by adjuvant chemotherapy either given intravenously, intraperitoneally, or both [52].
- Progression-free and overall survival is improved when minimal or no macroscopic disease remains at the end of primary surgery [53].
- Extensive debulking procedures are not without extensive morbidity.
- Some patients with advanced disease on presentation are unwell with weight loss, abnormal blood chemistry, thrombophilia, and concurrent medical disorders, all of which predispose to substantial operative complications and mortality. Many of these patients are not selected for clinical trials.
- There is no fool proof method to predict which patients are likely to attain an "optimal" status following surgery.
- Optimal debulking rates vary across centers and across countries.
- Patients with advanced ovarian cancer are more likely to reach an optimal status if operated on by a gynecological oncologist.

The debate as to whether patients presenting with advanced disease have similar outcomes if given up-front chemotherapy and then subjected to surgery is not new, yet still remains unresolved. Like all controversies in medicine, this lack of agreement emanates from the lack of acceptable Level 1 evidence on which to make sound clinical decisions. The rationale for giving chemotherapy up front prior to surgery is to help increase the chance of optimal debulking, which theoretically in this situation may improve survival, and also to reduce the morbidity associated with potential ultraradical surgical procedures. Patients who receive chemotherapy up front and do not show response or progress on the initial treatment have a very poor prognosis. These patients could thus be potentially spared from an unnecessary surgical procedure. However, what is not clear is whether these patients would also have fared badly by undergoing up-front surgery or indeed whether they would have fared better and actually represent the cohort of patients who above any would have benefited from a standard approach. The concept of such "chemo selection" of cases is indeed fraught with numerous unvalidated assumptions.

Interval debulking surgery after chemotherapy has been practiced for decades and was initially used when patients presented after having suboptimal primary debulking surgery. Van der Burg and colleagues performed a phase III randomized trial in an attempt to answer the question of whether patients who had suboptimal primary surgery and postoperative chemotherapy would benefit from a further attempt at debulking surgery [15]. This large EORTC study favored the group that had further debulking surgery after chemotherapy, as there was a significant increase in the progression-free and overall survival. The risk of death was reduced by one third after adjustment for a variety of prognostic factors. However, these results could not be reproduced by the Gynecology Oncology Group who performed a similar study (GOG 152) and published their results in 2004 [54]. The GOG study found no improvement in progression-free and overall survival for patients with advanced ovarian cancer in whom interval debulking surgery was performed after postoperative chemotherapy because of an unsuccessful primary cytoreduction. There are identifiable differences between these two studies that explain their discrepant results. In the EORTC study, the majority of the primary surgeons were general gynecologists and general

surgeons unlike the GOG study. This could explain why there were only about 30 % of patients who had residual disease less than 5 cm in the EORTC study compared to the GOG study where there were 55 %. Thus, one of the conclusions from the GOG 152 study was that if the primary surgery was performed by a trained gynecological oncologist and the tumor was deemed unresectable to less than 1 cm residual disease, then there was very little value in performing interval debulking surgery after a few cycles of chemotherapy. The other differences between these two studies were the type of chemotherapy used and the percentage of stage IV patients in the EORTC study which may have skewed the results to favor the interval debulking surgery group. The chemotherapy used in the GOG study was cisplatin and paclitaxel, which is consistent with current standards of care, unlike the EORTC study which used cyclophosphamide and cisplatin, a now outdated regimen. Suboptimal surgery with suboptimal cytotoxic chemotherapy is a recipe for disaster.

Recently an EORTC-led study attempted to answer a slightly different question as to whether there was any difference in progression-free and overall survival between patients who had an up-front primary debulking procedure followed by chemotherapy compared to patients who had neoadjuvant chemotherapy followed by interval debulking surgery in "extensive" (more than 60 % of cases operated on up front had metastatic disease measuring greater than 10 cm at baseline) stage IIIC–IV ovarian, fallopian tube, and peritoneal cancer. Patients with stage IIIC disease had to have abdominal disease and nodal disease alone was an exclusion criterion [1]. This large international multicentre phase III study reported no difference in progression-free survival (12 months) and overall survival (30 months) in either group when the tumors were debulked to ≤1 cm residual disease either up front (19 %) or after chemotherapy (51 %). Importantly, however, patients with disease 5 cm or less at baseline (about 80 % of the study population who were randomized to primary surgery) fared better with up-front surgery, with a statistically significant improvement in progression-free and overall survival compared to those who received neoadjuvant chemotherapy. Like many large randomized studies, the generalizability of the findings is still debatable, particularly since there was a huge disparity in surgical outcomes across the study, and indeed a test for heterogeneity was significant across countries suggesting a major disparity in surgical expertise and in patient selection for the study. Chi and colleagues in 2011 reported their experience treating patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma with primary debulking surgery during the same time period as the randomized EORTC-NCIC trial [55]. They reported much better survival figures for patients who had up-front optimal cytoreduction with residual disease ≤1 cm. In this series, progression-free survival was reported to be 17 months and overall survival over 50 months. A recent Cochrane review has, however, highlighted the lack of randomized data or even well-designed cohort studies showing the benefit of ultraradical surgery [21].

Radiological imaging in the form of CT and MRI scans and raised tumor markers such as CA125 levels have been used to help decide which patients are not suitable for up-front surgery. The presence of large-volume disease in the upper abdomen (diaphragm, porta hepatis) and mesentery of bowel raised levels of CA125 (≥500 U/ml), and low serum albumin are all factors that limit the ability to perform successful up-front surgery. However, imaging modalities have not been able to accurately predict these patients and that is why many centers now use diagnostic laparoscopy instead to help make these decisions [56–58]. On the face of it, using the laparoscope seems attractive in terms of evaluating the amount of tumor on the omentum, diaphragms, and bowel mesentery, but it takes a very skilled laparoscopic surgeon to decide which patients can or cannot be debulked [59–61]. Most experienced gynecological oncology surgeons will have come across situations where tumors that were deemed unresectable have gone on to have optimal debulking surgery. Furthermore, assessment of disease around the porta hepatis is all but impossible. Appropriately, a randomized trial to assess the utility or otherwise of laparoscopy in this setting is underway in the Netherlands [62].

What is not controversial in advanced ovarian cancer is the observation that if we could identify preoperatively which patients have good or bad tumor biology as reflected in chemosensitivity or even operability, this would give us the clue to help decide which tumors we should be operating on with maximal surgical effort and, conversely, in which patients up-front chemotherapy would be optimal. Unfortunately there is currently no tool available to help us differentiate these patients. Most likely, we will have these answers in the near future with the rapid development of tumor banking and translational research which will enable us to have better prognostic markers to dictate optimal treatment for each individual patient rather than a blanket approach.

In conclusion, up-front primary debulking surgery with the aim of removing all macroscopic disease or at least reducing residual tumor volume to ≤1 cm is still the standard of care for patients with stages IIIC–IV ovarian, fallopian tube, and peritoneal cancer. Progression-free survival and overall survival figures have been consistently better in retrospective and prospective series when patients are managed in this way. Selected patients may be considered for neoadjuvant chemotherapy but this should not be considered as the preferred approach.

Concluding Comments

This controversy is an important one for patients. Trials are still needed to answer a number of questions.

- Is it possible to define objective criteria to select which patients are best treated by up-front primary surgery and which by neoadjuvant chemotherapy?
- What is the optimum neoadjuvant chemotherapy regimen? For example, what is the role of dose-dense platinum-taxane regimens, angiogenesis inhibition (and other targeted therapies), and intraperitoneal therapy in this setting?
- What therapy if any should be used in those women who fail neoadjuvant chemotherapy?
- Can outcomes be improved by modifying the postoperative chemotherapy component?
- In those patients who achieve a complete clinical, imaging, and biochemical response to neoadjuvant chemotherapy, is there any value in operating and, therefore, is there a role for a trial comparing primary surgery followed by postoperative chemotherapy with primary chemotherapy alone, particularly in patients who do not have a pelvis mass?
- Finally, given the ongoing concerns about generalizability of the results of EORTC 55971-NCIC trial, can we design an optimal trial to definitively establish the role of neoadjuvant chemotherapy in patients fit to undergo surgery and, importantly, in such a trial how do we control for surgical variation?

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Does Intraperitoneal Therapy for Ovarian Cancer Have a Future?

14

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Summary Points

- Understanding current limitations of the "pharmacologic advantage," proposed mechanisms of IP drug delivery, and patient selection criteria.
- Treatment modifications to improve safety and tolerability.
- Integration with newer treatment approaches.

Introduction

Among women in the United States, ovarian cancer is the fifth leading cause of cancer-related mortality and is associated with more deaths than other female reproductive cancers [1]. Although the incidence of ovarian cancer varies among different countries, the overall case-fatality ratio is high (approximately 60 %) regardless of geographic region, suggesting that the impact of tumor biology remains predominant, limiting the impact of technical advances and new treatment strategies over the last 35 years. Following staging and cytoreductive surgery, patients generally receive systemic chemotherapy with an intravenous (IV) platinum/taxane doublet, which has remained a reasonable and well-tolerated standard of care for over a decade [2].

Although most ovarian cancer patients achieve clinical complete remission with their initial treatment, the majority develop recurrent disease and progressive chemotherapy resistance, which contributes to the high frequency of disease-related mortality. Clearly, small-volume, or microscopic, disease can persist after initial treatment and is responsible for disease recurrence. Any intervention that effectively addresses small-volume residual disease will thus have the potential to significantly improve long-term disease outcomes. In this chapter, we will review data supporting intraperitoneal (IP) therapy as one such effective treatment, considering potential reasons why it has not been universally embraced as a standard treatment and reviewing efforts to improve tolerability and acceptance of IP therapy while maintaining or improving efficacy.

Rationale for IP Chemotherapy

The peritoneal cavity is the major site of disease burden in ovarian cancer [3, 4]. While distant (hematogenous) dissemination can occur, ovarian cancer more commonly disseminates via shedding of tumor cells from the ovary into the surrounding peritoneal cavity. Circulation of these cells throughout the abdomen and pelvis provides an opportunity for serosal or peritoneal implantation, followed by varying degrees of invasion, fibrosis, and tumor-associated angiogenesis.

While the intensity of IV chemotherapy is limited by systemic toxicity, principally bone marrow suppression and neuropathy, several drugs with demonstrated activity in ovarian cancer can be administered directly into the peritoneal cavity [5]. Following cytoreductive surgery and IP drug administration, local tissues will experience prolonged exposure to higher concentrations of antitumor agents, while normal, extraperitoneal tissues, such as the bone marrow, will be relatively spared, depending on the specific kinetics of drug absorption, metabolism, and recirculation. For many drugs commonly used in the treatment of ovarian cancer, IP administration will provide a substantial local pharmacokinetic advantage over IV administration.

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Surgical Issues

While spread of ovarian cancer within the peritoneal cavity is common at diagnosis, the disease is frequently amenable to cytoreductive surgery, which is most commonly performed at initial diagnosis, prior to administration of chemotherapy. It is unusual among solid tumors for surgery to have such a key role in the management of widespread disseminated disease. However, a large number of retrospective studies over the last 35 years have demonstrated an inverse correlation between volume of tumor remaining at the completion of initial surgery and overall survival [6]. These retrospective data do not establish cause and effect, and it remains difficult to distinguish between favorable tumor biology compared to increased surgical skill. However, the consistency of these observations has led to the goal of complete cytoreduction to no macroscopic visible disease with initial diagnostic surgery. A meta-analysis has also demonstrated the prognostic importance of cytoreduction. Both overall survival (OS) and progression-free survival (PFS) were significantly prolonged in women without visible residual disease at completion of initial surgery. When patients with visible residual disease were evaluated, survival estimates remained statistically significant in favor of optimal residual disease to 1 cm or less compared with those with suboptimal residual disease greater than 1 cm [7].

Today, approximately 80 % of patients will have optimal residual disease after primary cytoreductive surgery, and about 25 % will achieve cytoreduction to the level of microscopic residual disease, the most favorable category. Taken together, the tendency for ovarian cancer to remain within the peritoneal cavity, the ability to achieve small-volume or microscopic residual disease in the majority of patients, and the availability of active agents that can be administered IP provide a strong rationale for the use of IP therapy in this disease.

Historical Context

IP chemotherapy was first used for palliation of malignant ascites associated with various intra-abdominal tumors. As early as 1955, researchers demonstrated the safety and efficacy of IP therapy in patients with ovarian cancer. IP nitrogen mustard was administered to seven ovarian cancer patients with malignant ascites and effusions. This treatment was tolerable and associated with a significant decrease in ascites in six of the seven patients [8]. Additional research in the 1960s and 1970s by Speyer and Dedrick at the NIH established the basic pharmacologic and pharmacokinetic principles and early guidelines for IP therapy [9]. In subsequent years, Markman and Howell established the safety and efficacy of IP cisplatin, a drug that rapidly became the backbone of therapy for ovarian cancer [10]. The development and subsequent refinement of permanent indwelling peritoneal catheters allowed for safe and reliable repeated administration of IP therapy. These advances led directly to the ability to study IP administration of cisplatin and other active agents in phase I, phase II, and phase III clinical trials in ovarian cancer.

Pharmacokinetic Principles

Over the last three decades, important observations have been made regarding the impact of IP therapy in ovarian cancer. The first is that tumors have a complex microenvironment that includes malignant cells, normal cells, and an extracellular matrix that all influence the distribution and sensitivity to anticancer drugs. In addition, intraperitoneal tumor deposits are frequently associated with fibrosis, adhesions, and loculated compartments [11]. These normal findings are accentuated in patients with prior abdominal surgery or perioperative complications, limiting the effectiveness of IP drug administration. While contrast-based imaging techniques (CT and nuclear scans) have been used to assess perfusion of the peritoneal space, these tests involve an IP injection, as well as financial expense, and are not highly predictive of peritoneal circulatory dynamics.

In order for a drug to be effective, it must circulate freely and then penetrate multiple layers of cells to achieve local cytotoxic concentrations [12]. When a drug is administered IP, it will penetrate the tumor both by diffusion into the tumor from the free surface in the peritoneal cavity and via capillary recirculation after the drug enters the systemic circulation [13]. Physicochemical properties of drugs such as molecular weight, shape, charge, and aqueous solubility determine the rate of diffusion through tissue [11, 14]. In addition, some drugs are administered as inactive prodrugs that require in vivo conversion to reactive intermediates. This includes cyclophosphamide, which is hydroxylated in the liver, and platinum compounds, which require local aquation with detachment of chloride (cisplatin) or organic (carboplatin) leaving groups. Perhaps most importantly, tumors generally have immature “leaky” capillaries combined with the absence of normal lymphatics, resulting in markedly elevated interstitial pressures, which form an uphill barrier to drug penetration and diffusion within tumor nodules.

Thus, the kinetics of drug absorption into the systemic circulation and efficiency of penetration into tumor after IP administration will be different for every drug. It should not be surprising that drugs will penetrate more poorly into large tumors where interstitial drug concentration will be more dependent on vascular delivery of drug. For this reason, randomized trials of IP therapy in ovarian cancer have largely been limited to patients with small-volume (optimal) residual disease after primary cytoreductive surgery.

Based on these factors, an ideal agent for IP administration is one that is very effective against ovarian cancer when administered systemically, capable of tumor penetration via passive diffusion or carrier-mediated transport, able to remain in an active form within the peritoneal cavity for prolonged periods of time, and with a low incidence of local and systemic adverse effects [5].

However, these recommendations assume that we actually understand how IP therapy achieves benefit in women with ovarian cancer. There is a unique relationship between ovarian cancer and the peritoneal microenvironment, reflected by the propensity for widespread dissemination of peritoneal implants without deep invasion or hematogenous spread, as well as the prominent role of vascular endothelial growth factor (VEGF) in tumor-associated angiogenesis. For example, it is possible that direct administration of chemotherapy could alter the normal peritoneal environment to block tumor implantation, or impede the development of tumor-associated blood vessels, rather than mediate direct cytotoxic effects against existing tumor deposits. Along these lines, there is some evidence that patients who receive IP therapy are more likely to relapse in retroperitoneal nodes or distant sites, rather than within the peritoneal cavity, suggesting that the biologic behavior of the disease could be altered.

What Is the Evidence to Support the Use of Intraperitoneal Therapy as First-Line Treatment of Ovarian Cancer?

The pharmacokinetic characteristics of IP chemotherapy have been defined for a number of agents, as illustrated in Table 14.1 [15]. Information from these studies provided the basis for three North American randomized phase III trials comparing IV with IP chemotherapy for initial treatment of ovarian cancer (Table 14.2).

Table 14.1 Pharmacologic parameters for IP drug administration

Drug name	Molecular weight	Physical properties	Ratio (peritoneal-plasma)	
			Peak	AUC
Cisplatin	300.05	Water soluble, very high protein binding (>95 %), more rapid activation (compared to carboplatin)	20	12
Carboplatin	371.25	Water soluble, very low protein binding, slower activation (compared to cisplatin)	24	10–18
Topotecan	457.91	Water soluble, 35 % protein bound		54
Mitomycin	334.33	Vesicant	71	
Melphalan	305.20	Water soluble	93	65
Methotrexate	454.44	Water soluble	92	100
Docetaxel	861.94	Water soluble, very high (>98 %) protein binding		181
5-Fluorouracil	130.08	Water soluble	298	367
Doxorubicin	543.53	Water soluble salt, vesicant, high (70 %) protein binding	474	
Gemcitabine	299.66	Water soluble, low (<10 %) protein binding		759
Paclitaxel	853.92	Requires lipid/alcohol formulation, high (90 %) protein binding		1,000
Mitoxantrone	517.40	Water soluble, vesicant, high (78 %) protein binding		1,400

Adapted from [15]

Table 14.2 Completed GOG phase III trials of intraperitoneal chemotherapy

Study	Treatment regimen		Patients		Median OS (months)			
	Control	Experimental	Eligibility	*N*	Contl	Exptl	*P* value	Reference
SWOG8501 GOG104	Cisplatin 100 mg/m^2 IV Cyclophosphamide 600 mg/m^2 IV (q 21 days×6)	Cisplatin 100 mg/m^2 IP Cyclophosphamide 600 mg/m^2 IV (q 21 days×6)	Stage III ≤2 cm residual	546	41	49	0.02	[16]
GOG114 SWOG9227	Cisplatin 75 mg/m^2 IV (D1) Paclitaxel 135 mg/m^2 IV (24 h D2) (q 21 days×6)	Carboplatin (AUC9) IV (q 28 days×2) then Paclitaxel 135 mg/m^2 IV (24 h D1) Cisplatin 100 mg/m^2 IP (D2) (q 21 days×6)	Stage III ≤1 cm residual	462	51	63	0.05	[18]
GOG172	Cisplatin 75 mg/m^2 IV D1 Paclitaxel 135 mg/m^2 IV (24 h D2) (q 21 days 3×6)	Paclitaxel 135 mg/m^2 IV (24 h D1) Cisplatin 100 mg/m^2 IP (D2) Paclitaxel 60 mg/m^2 IP (D8) (q 21 days×6)	Stage III ≤1 cm residual	415	49	67	0.03	[19]

The first randomized trial was conducted by the Southwest Oncology Group (SWOG 8501) and the Gynecologic Oncology Group (GOG 104) [16]. In this trial, patients with small-volume residual disease (≤2 cm) were randomized to receive six cycles of IV cyclophosphamide (600 mg/m^2) plus 100 mg/m^2 of cisplatin either IP or IV every 3 weeks for six cycles. Among the 546 eligible patients, the estimated median survival was significantly longer in the IP group (49 months; 95 % CI 42–56) compared to the IV group (41 months; 95 % CI 34–47). The hazard ratio (HR) for the risk of death was 0.76 (95 % CI 0.61–0.96; $P=0.02$) in favor of IP therapy. Although moderate to severe abdominal pain was more frequent in the IP group, grade 3/4 granulocytopenia and tinnitus, clinical hearing loss, and grade 2–4 neuromuscular toxic effects were significantly more frequent in the IV group.

GOG 104 offers the cleanest comparison of IV and IP therapy, as all patients received the same dose of cyclophosphamide and cisplatin, with variation only in the route of administration of the cisplatin. In this trial, an equal number of patients on the IV and IP arms (58 %) were able to receive all 6 cycles of assigned therapy. This trial allowed patients with up to 2 cm residual disease to be entered, reflecting the definition of optimal cytoreduction at that point in time. More recent trials have utilized 1 cm as the cutoff to define optimal residual disease. Accrual on GOG 104 was extended to allow additional patients with microscopic residual disease, the group hypothesized to show the greatest benefit for IP therapy. While the overall study demonstrated a statistically significant survival benefit, it is interesting that no statistically significant survival benefit was shown for the minimal residual disease subgroup. However, this could be attributed to the overall good prognosis of that population, regardless of treatment. The results of this study were published in 1996, the same year as GOG 111, the seminal trial documenting the efficacy of paclitaxel in ovarian cancer [17], and there was considerable diversion in opinion regarding the relative importance of IP therapy or the incorporation of paclitaxel.

A second IP trial, SWOG 9927/GOG 114, randomized 426 patients to either a control regimen of IV paclitaxel 135 mg/m^2 over 24 h followed by IV cisplatin 75 mg/m^2 every 3 weeks for six cycles or an experimental regimen of two doses of high-dose IV carboplatin (AUC 9) every 28 days for two cycles followed by six cycles of IV paclitaxel 135 mg/m^2 over 24 h followed by IP cisplatin at 100 mg/m^2 every 3 weeks (total of eight cycles of therapy) [18]. It was hypothesized that the two carboplatin cycles would "chemically" cytoreduce residual tumor before instituting IP therapy. This trial demonstrated improved PFS (median 28 versus 22 months; relative risk 0.78; log rank $P=0.01$) and OS (median 63 versus 52 months; relative risk 0.81; $P=0.05$) in favor of the IP group. Toxicities greater than or equal to grade 3, including neutropenia, thrombocytopenia, and gastrointestinal and metabolic toxicities, were significantly more frequent in the IP group.

While both arms of this study included paclitaxel, interpretation of clinical outcomes was limited by the multiple differences in treatment between the two arms, and it was uncertain whether the initial high-dose carboplatin, IP cisplatin, or both contributed to improved outcomes. It is not surprising that toxicities, particularly myelosuppression, were greater in the experimental arm. The two cycles of high-dose carboplatin likely contributed to difficulty administering subsequent therapy. Overall, 18 % of patients randomized to the experimental arm received less than two courses of IP therapy.

In the third trial, GOG 172, a total of 417 eligible patients with optimally debulked stage III ovarian cancer were randomized either to IV paclitaxel (135 mg/m^2 over 24 h) followed by IV cisplatin (75 mg/m^2) or to a hybrid arm of IV paclitaxel (135 mg/m^2 over 24 h) followed by IP cisplatin (100 mg/m^2), plus IP paclitaxel (60 mg/m^2) on day 8 [19]. Both treatments were repeated every 21 days for six cycles. There were significantly more patients with grade 3 and 4 leukopenia, thrombocytopenia, and gastrointestinal toxicity, renal toxicity, neurologic toxicity, fatigue, infection, metabolic toxicity, and pain toxicity in the IV/IP arm compared to the IV arm. Because of these toxicities and/or catheter problems, 48 % of patients in the IP arm received three or fewer IP treatment cycles, and only 42 % patients received all planned six cycles of IP therapy. Nonetheless, the trial demonstrated improved PFS (median 24 versus 18 months; relative risk 0.80; log rank $P=0.05$) and OS (median 66 versus 50 months; relative risk 0.75; $P=0.03$) in favor of the IV/IP group. This remains the longest reported survival to date from a randomized trial in advanced ovarian cancer, and the magnitude of improvement associated with IP/IV chemotherapy appears similar to that observed with the introduction of either cisplatin or paclitaxel.

Hazard ratios for PFS and OS are illustrated in Fig. 14.1. The potential impact of IP therapy has also been evaluated through a meta-analysis of randomized trials, confirming improvement in PFS and OS [20].

Why Is the Concept of Intraperitoneal Therapy Still Controversial, and What Are the Barriers to Its Use?

GOG 172 was carefully conducted, with important clinical outcomes, and also raised relevant questions that are being addressed in ongoing trials. Due to patient selection criteria and the limited adoption of IP therapy, the trial was open to accrual for 5 years. During this period of time, the standard of care was rapidly evolving from cisplatin and 24-h

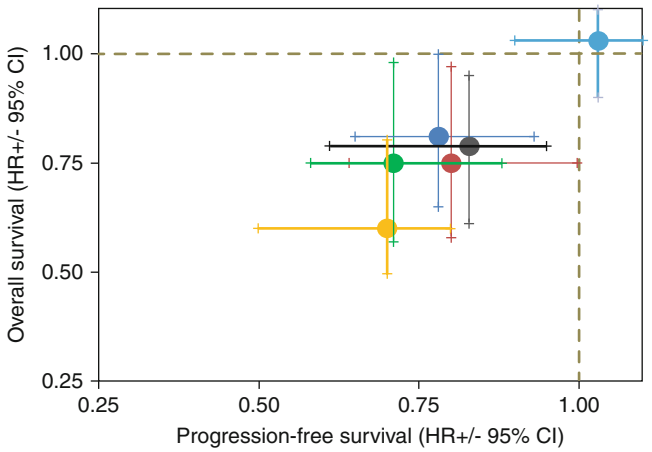

Fig. 14.1 Hazard ratios (HR ± 95 % confidence intervals) for OS and PFS from trials of intraperitoneal therapy (GOG 104, 114, and 172). For comparison, representative data are included to illustrate positive (JGOG 3016, GOG 111) and negative (GOG 0182) outcomes using intravenous chemotherapy (16–19, 35, 40)

paclitaxel to carboplatin with 3-h paclitaxel, although results from GOG 158 demonstrating equivalent outcomes with lower toxicity from the paclitaxel carboplatin regimen were not published until 2 years after accrual to GOG 172 was completed [21] and subsequently adopted during a consensus conference of the Gynecologic Cancer InterGroup (GCIG) [2]. Nonetheless, there was some concern that GOG 172 utilized an "outdated" control arm, an exploratory cross-trial analysis suggested that future trials should compare IP therapy to IV carboplatin and paclitaxel [22], and it was argued whether or not IP therapy remains "experimental" [23, 24].

A more significant concern was the increased frequency and severity of dose-limiting toxicity seen on the IV/IP arm of GOG 172, resulting in a substantial number of patients being unable to complete the assigned IV/IP therapy. Most toxicities were short term, and there were no differences with regard to treatment-related deaths or quality of life at 1 year [25]. An exception was neurotoxicity, which improved after completion of treatment on both arms of GOG 172 but remained higher 1 year after completion of treatment on the IV/IP arm [26]. Most likely, this can be attributed to the higher dose of IP cisplatin at 100 mg/m^2.

It has been more than a decade since accrual to GOG 172 was completed. Since that time, there have been significant improvements in supportive care for patients receiving chemotherapy, including familiarity with catheter placement techniques and management of catheter-related complications [26]. With the use of contemporary antiemetics and growth factors, a higher proportion of patients can successfully complete a full regimen of IV/IP chemotherapy, similar to GOG 172 [27].

The results of this trial were reported on an intent-to-treat basis. The finding that the majority of patients were not able to complete all six prescribed cycles of IV/IP therapy has raised questions regarding the correlation between clinical outcomes and amount of IV/IP therapy. A clinically meaningful survival advantage was observed despite the limited number of IV/IP cycles administered, and one could hypothesize that either a substantial benefit occurs within the earliest cycles of treatment or that even greater benefits might be seen if more patients were able to complete the prescribed therapy. One must be cautious in attempting to correlate clinical outcomes with the number of IP/IV cycles delivered, as it is possible that adverse prognostic factors might negatively impact the ability to complete the assigned therapy. A recent long-term follow-up analysis of GOG 114 and GOG 172 showed that those who completed five or six cycles of IV/IP therapy had improved survival compared to those who received fewer cycles [28]. However, this might also reflect underlying favorable prognostic factors and does not establish cause and effect.

Are Treatment Modifications the Answer to Introducing Intraperitoneal Therapy More Widely in Clinical Practice?

A number of treatment modifications have been examined to decrease toxicity and improve patient tolerability, including alterations in cisplatin dosage, sequence of drug administration, substitution of carboplatin, and a reduction in paclitaxel infusion duration. While many of these changes are based on prospective data from IV chemotherapy trials, they have not generally been validated with IP chemotherapy, and there will remain concern that such modifications could have a negative impact on overall efficacy. If we knew which components of IP chemotherapy were essential to achieve optimal outcomes, it would be easier to make adjustments, but this has yet been established.

Schedule and Duration of Paclitaxel

Many institutions do not have the capacity, and cannot justify the cost, to admit patients for a 24-h infusion of paclitaxel, as used in GOG 114 and 172. Thus, there has been increased utilization of a 3-h paclitaxel infusion. However, when given IV followed by IV cisplatin, 3-h paclitaxel was associated with unacceptable neurologic toxicity [29]. Thus, many will continue to give the subsequent IP cisplatin on day 2, approximately 24 h after IV paclitaxel. Of note, while absorbed fairly rapidly, the kinetics of IP cisplatin result in a blunted peak plasma concentration with prolongation of systemic exposure [30], and it is likely that

the risk of neurologic toxicity in combination with same-day paclitaxel would be reduced with IP cisplatin.

Reduction in Cisplatin Dosage

Multiple randomized trials have failed to document an improvement in the median OS associated with increased dose, dose-intensity, cumulative dose delivery, or number of cycles of cisplatin and carboplatin. Many clinicians prefer to utilize cisplatin at 75 mg/m^2 (IV or IP) compared to 100 mg/m^2 to avoid excessive non-hematologic toxicity. However, this is based on the assumption that a 25 % reduction in dose would not compromise the therapeutic advantage associated with IP cisplatin at 100 mg/m^2. The optimal dose of IP cisplatin is unknown, and there are no randomized trials that are directly comparing different dose levels of IP cisplatin.

Substitution of Carboplatin

When given IV, carboplatin clearly has less non-hematologic toxicity than cisplatin [20], and there has been considerable interest in the substitution of IP carboplatin for IP cisplatin. Early studies, without optimized dosing for area under the curve (AUC) of concentration and time, suggested that carboplatin was inferior to cisplatin when administered IP [31, 32]. Howell and colleagues have recently shown in animal models that cisplatin produces a 3.4-fold higher level of platinum in tumor nodules when compared to an equimolar dose of carboplatin. However, when cisplatin and carboplatin were injected at equitoxic doses, tumor platinum levels were equivalent. Although they found that platinum concentrations in equal-sized nodules were highly variable, tumor platinum content decreased with increasing nodule size following IP cisplatin but not with equitoxic doses of IP carboplatin. These results suggest that clinically, IP carboplatin may have comparable or better drug penetration when compared to cisplatin when given at equitoxic doses. However, these models do not clearly distinguish between direct tumor penetration and absorption followed by systemic recirculation, which occurs very rapidly with platinum agents in murine tumor models. In addition, there is a theoretical concern related to the relatively slow rate of activation of carboplatin, compared to cisplatin, due to the nature of the organic leaving groups. These data, along with the more favorable toxicity profile of carboplatin, provide support for examining carboplatin in place of cisplatin in the IP treatment of patients with ovarian cancer [13].

Miyaga and colleagues examined detailed kinetics of IV and IP carboplatin administration. They found that the platinum AUC in the serum was exactly the same no matter which route of administration was used. This equivalency of AUC dosing is an interesting observation and suggests that carboplatin is absorbed fairly rapidly from the peritoneal cavity and then cleared systemically via the kidneys, "as if" it was given by IV infusion. However, the platinum AUC in the peritoneal cavity was approximately 17-fold higher when carboplatin was administered IP. Thus, IP carboplatin administration provides a higher intraperitoneal platinum AUC while attaining the same intravenous platinum AUC as that obtained with IV carboplatin administration [33]. Similar AUC and clinical data were obtained from a GOG phase I trial of IP carboplatin in previously untreated patients [34]. Two phase III trials of IP versus IV carboplatin are being conducted by GOG (GOG 252, described below) and the Gynecologic Oncology Trial and Investigation Consortium in Japan (GOTIC 001) in collaboration with the Japanese Gynecologic Oncology Group (JGOG 3019).

Role of Weekly Paclitaxel

A further question is whether the survival advantage seen with IV/IP therapy in GOG 172 could be due to the addition of day 8 paclitaxel rather than the IP delivery of cisplatin and paclitaxel. This question is particularly relevant given the recent JGOG data in support of weekly, dose-dense paclitaxel in the treatment of ovarian cancer [35]. This question was partially addressed in GOG 252, which completed accrual in 2011, and is expected to report primary data in 2014. This three-arm trial includes a modified regimen of cisplatin-based IP chemotherapy (with cisplatin at 75 mg/m^2 and paclitaxel administered over 3 h), compared to IV carboplatin with weekly dose-dense paclitaxel and IP carboplatin with weekly dose-dense paclitaxel [36]. This trial will provide a clean comparison of IV and IP carboplatin and the opportunity to compare IP carboplatin and IP cisplatin. However, the cisplatin arm uses a different dose and schedule of paclitaxel administration (variation of GOG 172), and all regimens incorporate bevacizumab, which could complicate the assessment of differences related to chemotherapy. Although the majority of patients on GOG 252 had optimally cytoreduced disease, the protocol also permitted enrollment of approximately 125 patients with suboptimal residual disease, providing the first randomized experience with IP therapy in a population with more extensive intraperitoneal tumor.

Neoadjuvant Chemotherapy

For patients with large-volume disease, extensive ascites, and/or comorbidities, there is increasing utilization of neoadjuvant chemotherapy for three cycles, followed by consideration of interval cytoreductive surgery. With this sequential

approach, at least half of the patients will achieve optimal small-volume residual disease, and these patients could be considered for three cycles IP chemotherapy after recovering from cytoreductive surgery. Of note, the NCI Canada Clinical Trials Group (NCI-CTG), in collaboration with the Gynecologic Cancer InterGroup, is currently conducting a randomized phase II-III trial to evaluate the safety and efficacy of this approach (OV 21/PETROC).

Complexity and Cost

There remains some reluctance among oncologists to fully embrace IP in spite of the documented clinical efficacy. As already discussed, potential hurdles include increased toxicity, technical expertise, and the risk of complications associated with catheter placement. Adoption has been more rapid in larger treatment centers and major academic institutions with increased availability of multidisciplinary team support. This has led to the consideration that the care of patients with ovarian cancer, including the utilization of IP chemotherapy, might be best delivered at institutions with more experience in the management of ovarian cancer. Indeed, in a retrospective analysis, ovarian cancer survival has been shown to be correlated with hospital and surgeon volume [37].

As currently administered, IP therapy is generally more costly and time consuming. It requires increased staff time and training and, with cisplatin, requires additional time for proper pre- and post-cisplatin hydration. Nonetheless, analyses have shown that IP therapy has a favorable cost-effectiveness profile, particularly when long-term outcome improvement is considered [38]. With GOG 172, including 24-h paclitaxel, inpatient treatment accounted for over 40 % of the cost of IP/IV chemotherapy. Development and validation of an ambulatory regimen with equivalent therapeutic efficacy would provide even greater cost-effectiveness [39].

Future Directions

In addition to improving the safety and tolerability of IP treatment regimens, there are a number of other opportunities that could further enhance clinical outcomes, including the incorporation of targeted molecular agents (IV and IP), and strategies to promote a local immune response. Ongoing studies have already incorporated bevacizumab (GOG 252), and studies are planned with multi-targeted receptor tyrosine kinase inhibitors and inhibitors of poly-ADP ribose polymerase (PARP). These targeted treatment strategies will generally be applied in a similar manner regardless of whether the primary chemotherapy is administered IP or IV. As a result, there is also a trend for large randomized trials to permit patient election of IP or IV chemotherapy, with stratification prior to randomization, unless the chemotherapy is the primary question being addressed in the trial. This inclusive design makes it easier to broadly enroll the majority of patients with newly diagnosed disease and should facilitate more rapid completion of high-priority research studies.

While tumor-associated angiogenesis is an important target, emerging data suggest that blockade of VEGF-mediated signaling may have greater potential for clinical benefit in the setting of large-volume high-risk disease, or recurrent disease associated with ascites, rather than the typical patient referred for IP therapy with small-volume optimal residual disease following primary cytoreductive surgery. Strategies to reverse drug resistance through targeting of DNA repair, such as PARP inhibition, may prove beneficial regardless of the extent of residual disease, and data from planned studies should address these questions in the future.

Studies are also needed to evaluate the expanded utilization of IP therapy in other patient populations. For example, patients with larger-volume (>1 cm) tumors following surgery might benefit from IP therapy, either as primary treatment or following neoadjuvant therapy with interval cytoreduction, and these points are incorporated within ongoing randomized trials. Other potential scenarios for IP studies include early stage disease, recurrent disease, or in the palliation of end-stage symptoms such as refractory ascites.

Finally, studies will hopefully provide more rigorous assessment regarding the impact of IP treatment modifications to improve safety and tolerability, as in GOG 252. However, it is unlikely that substantial funding will be available to conduct large randomized trials to address these modifications, which are based on the use of generic chemotherapy agents without new sponsorship from the pharmaceutical industry or national cooperative groups. Instead, it is likely that these questions will be addressed through secondary study endpoints and analysis (and meta-analysis) of subpopulations, with or without prospective randomization of treatment.

Conclusions

IP therapy is not a new concept, but it has clearly demonstrated improved clinical outcomes when used as front-line treatment for advanced-stage ovarian cancer based on randomized phase III clinical trials. Integration of IP therapy into standard oncologic practice has been somewhat slow to materialize, at a national and international level, and many significant questions remain to be resolved, including optimal selection of drug and treatment paradigms. However, we have an obligation to make the best treatments available to our patients with advanced ovarian cancer. IP therapy is an appropriate treatment choice for

many patients, and we should have the capability and expertise to offer this treatment to our patients while providing them with the opportunity to collaborate on decisions regarding their care.

Does IP therapy in ovarian cancer have a future? Ovarian cancer remains a highly lethal disease, and thus far, the overall impact of any individual treatment strategy on long-term disease-related mortality has been quite limited. New strategies, and standards of care, will continue to evolve with incorporation of potential advances, such as weekly dose-dense scheduling of paclitaxel, regardless of the route of drug administration. The more that we understand about the biology of this unusual disease, and how to optimize treatment, the better our chances of defining critical pathways that will translate into a reduction in overall mortality.

Concluding Comments

- IP cisplatin-based chemotherapy has demonstrated clear evidence of improved outcomes in patients with small-volume residual disease following primary cytoreductive surgery.
- A variety of treatment modifications (to improve safety, tolerability, and patient selection criteria) are under evaluation in randomized trials.
- Optimal future development of IP chemotherapy, including integration with molecular targeted agents, awaits results from ongoing studies.
- Future trials are unlikely to randomize between IV and IP therapy but may include subpopulations of patients who elect to receive IP therapy.

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Maintenance Therapy for First-Line Treatment of Ovarian Cancer: Is This the Strategy for the Future?

15

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Summary Points

- The efficacy of maintenance intravenous taxane and platinum chemotherapy is still controversial in women with complete response after upfront standard chemotherapy. The impact on health-related quality of life and economic cost have not been considered.
- Based on efficacy in patients having progressed on standard schedule paclitaxel, dose-dense weekly paclitaxel would be intriguing to investigate in this setting.
- The results of two large randomized control trials have demonstrated significantly improved PFS in women who received bevacizumab with chemotherapy and then extended beyond the chemotherapy. However, optimal dose and duration of treatment, cost, toxicity, impact on quality of life, and selection of patients likely to benefit remain unanswered.

Introduction

Ovarian cancer is the fourth leading cause of cancer-related death among women [1]. More than 75 % of women are diagnosed at advanced stage, and less than 40 % of them are alive 5 years after the diagnosis [2]. Unfortunately, despite intensive research, the cure rate has remained almost unchanged over the last decades [3]. Primary treatment is based on maximal surgical cytoreduction followed by 6 courses of platinum- and taxane-based chemotherapy [4]. However, it is estimated that over 70 % of women with advanced stage epithelial ovarian cancer will experience a relapse of the disease in about 15–20 months after diagnosis [5]. Different strategies of treatment with the goal of reducing the recurrence rate have been evaluated including an increased number of cycles of primary chemotherapy [6, 7], the addition of new drugs to standard treatment [8], and/or the continuation of primary chemotherapy in patients without progression of the disease, described as *maintenance/consolidation therapy* [9–11]. This term is referred to a therapy added at the end of a predefined primary treatment, typically in responding patients. More specifically, consolidation would refer to agents not used in upfront therapy, while maintenance would refer to agents already used. The hypothesis is that by reducing the number of slowly dividing residual cancer cells inadequately exposed to initial cycle-dependent chemotherapy, a decreased risk of tumor growth is obtained. While this approach has been extrapolated from the treatment of lymphoblastic leukemia [12], maintenance/consolidation therapy in solid tumors still remains as a controversial strategy of treatment. Ideally, maintenance therapy should include drugs which can stop tumor growth for a long period of time, with few and tolerable adverse events, and which can offer an acceptable quality of life and cost-effectiveness ratio.

This chapter will detail the advantages and disadvantages of maintenance therapy in women affected by advanced stage epithelial ovarian cancer who obtain clinical response after primary treatment.

Pro Chemotherapy

Failure of some tumor cells to undergo apoptosis after standard frontline cytotoxic therapy may partially explain why the vast majority of women with advanced ovarian cancer ultimately progress and die from their disease. Thus, for the

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majority of women without evidence of disease (or without evidence of disease progression) after completing frontline therapy, one potentially effective strategy is the extension of treatment with cytotoxic regimens with the goal to clear residual tumor cells and preempt or significantly forestall the development of progressive/recurrent cancer.

Though there have been a paucity of controlled studies testing this general hypothesis, there is nonetheless evidence to support this approach, stemming from a joint Southwest Oncology Group and Gynecologic Oncology Group (SWOG-GOG) phase III trial [13]. Patients with a history of International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease in complete clinical, radiographic, and biochemical remission after receiving 5–8 cycles of platinum-taxane frontline therapy were randomly allocated to treatment with 12 versus 3 cycles of single-agent paclitaxel at 175 mg/m^2 administered every 28 days in 3-h infusions. The primary end point was progression-free survival (PFS), with a target sample size of 458 patients. The study was closed prematurely, when an interim intent-to-treat analysis demonstrated a PFS advantage for the prolonged paclitaxel cohort. An updated analysis reported in 2009 showed the hazard ratio for PFS to be 0.70 with a one-sided *p*-value of 0.008, with a median PFS shift from 14 to 22 months in favor of the prolonged over the abbreviated paclitaxel group [9].

Though a difference in OS was not detected, the analysis of OS was compromised by premature closure of the trial, insufficient power to show an effect on OS if one were present, and the potential that subsequent, non-protocol-defined use of subsequent therapy (including "crossover" to additional paclitaxel in the abbreviated treatment group) could have statistically neutralized any potential difference in OS that would have otherwise been observed. The latter issue is the basis for a recent consensus by the Gynecologic Cancer InterGroup (GCIG) that PFS is perhaps the preferred primary end point for frontline trials, including those with a maintenance component [14].

One criticism is that midway through the trial [13], the paclitaxel dose was reduced to 135 mg/m^2 due to a greater than expected rate of voluntary withdrawal. However, the modified regimen was acceptable to the vast majority of patients. In aggregate, the relative rates of grade 2 and grade 3 peripheral neuropathy were 18 % versus 14 % and 5 % versus 1 % in the prolonged versus abbreviated group. These incidence rates appear to be reasonable given the efficacy benefit.

Based on the results of this initial trial demonstrating proof of principle for taxane-based maintenance therapy, the GOG activated a second-generation phase III trial in a population with similar eligibility criteria, examining 12 monthly cycles of maintenance paclitaxel versus observation (control), with a primary end point of OS [15]. This is an ongoing two-arm trial, one experimental arm evaluating native paclitaxel and the other evaluating CT-2103, paclitaxel conjugated to a novel polyglutamate polymer which in itself is soluble in aqueous solution, can be administered over 10 min, and is hypothesized to have a more favorable toxicity profile (hypersensitivity, neurotoxicity, alopecia) than native paclitaxel solubilized with cremophor.

The antineoplastic benefit of paclitaxel and potentially other taxanes as an extension of standard primary therapy is biologically plausible. Paclitaxel's mechanism of action, the blockade of a normal mitotic spindle through its stabilization of tubulin polymers, is specific for the G2/M interface of the cell cycle [16]. Therefore, it stands to reason that the likelihood of eradicating all malignant cells within a heterogeneous population will increase with more frequent or prolonged exposure. Evidence supporting the efficacy of paclitaxel as a function of frequency has been demonstrated in studies of dose-dense weekly paclitaxel. A phase II trial of weekly intravenous paclitaxel at 80 mg/m^2 in women with recurrent, primarily platinum-resistant disease demonstrated an objective response rate of 21 % [17]. A phase III Japan Gynecologic Oncology Group frontline trial of carboplatin combined with either this dose-dense weekly paclitaxel regimen (experimental) or every 3-week administration at 175 mg/m^2 (control) for 6 cycles demonstrated a significant improvement in PFS (median of 28.0 months, 95 % CI 22.3–35.4 versus 17.2 months, 95 % CI 15.7–21.1, hazard ratio [HR] 0.71) and 3-year OS (72.1 % versus 65.1 %, HR 0.75) in favor of the experimental regimen in 631 women with stages II through IV disease [18]. An updated analysis, with median follow-up of 6.4 years, was consistent with the initial report. The median OS was 28.2 months for the dose-dense weekly group versus 17.5 months for the control group, HR 0.76 (95 % CI 0.62–0.91) [19]. A confirmatory trial conducted by the GOG has completed accrual but has yet to mature [20].

In summary, recognizing the limitations of standard frontline cytotoxic therapy for patients with advanced ovarian cancer, it will be important to build on success preliminarily demonstrated for maintenance paclitaxel. In addition, given the differential impact of dose-dense weekly administration, it would be intriguing to investigate this regimen extended beyond the conventional duration.

Con Chemotherapy

Primary treatment of patients with newly diagnosed advanced ovarian cancer is based on maximal upfront debulking surgery followed by six courses of carboplatin and paclitaxel [21]. Since the early 1990s, maintenance chemotherapy in patients with clinical and/or pathological response has been evaluated in isolated phase II–III randomized trials, by using several strategies with different drugs, schemes and route of administration. As a consequence, inconclusive results motivated its scarce implementation in clinical practice [21].

The first phase III randomized clinical trials tried to determine whether increasing the number of platinum-based cycles during frontline chemotherapy would improve OS rates [22–24]. These studies showed that prolonging chemotherapy beyond 5–6 cycles did not improve OS but significantly increased toxicity. The randomization, however, was performed before the initiation of frontline treatment, including the estimated 25 % of patients who would have been platinum resistant.

In addition, other phase III randomized trials have evaluated the efficacy of observation versus extended treatment by using intravenous topotecan [11, 25] and intravenous paclitaxel [10]. None of them demonstrated a significant improvement in PFS and OS.

Maintenance chemotherapy in women with complete response after completing primary treatment has remained highly controversial. As previously mentioned, the only phase III randomized trial suggesting possible benefit was conducted by the SWOG/GOG-178 [13]. Thus, intravenous taxane chemotherapy could be an attractive strategy given the additional demonstrated anti-angiogenic properties of this drug [26].

Many aspects of this trial, however, have been questioned. The study's design did not include a control arm and allowed patients to switch from the 3 cycles arm to the 12 cycles arm after the results of the interim analysis were reported. Moreover, if the free-interval time takes into consideration freedom not only from disease but also from chemotherapy and therefore is calculated from the end of maintenance treatment, then very similar results are achieved, with 10 and 11 months, in the 12 and 3 cycle arm, respectively. This means that paclitaxel does not cure more patients just delays recurrence but at the cost of continuous treatment and toxicity. The study design also permitted a dose reduction for patients with grade 4 neutropenia, grade 3/4 thrombocytopenia, or grade 2 neuropathy. This issue becomes relevant when the toxicity profile of the study is analyzed. They report only major differences in the incidence of treatment-related neuropathy, 15 and 23 % of grade 2–3 sensory neuropathy in women assigned to receive 3 or 12 cycles, respectively [13].

Perhaps most important is the fact that the total sample size was inadequate to make a definitive statement regarding the impact on OS, even in a long-term follow-up analysis. In 2007, an expert panel composed by the Food and Drug Administration (FDA), the American Society of Clinical Oncology (ASCO), and the American Association for Cancer Research (AACR) agreed that the impact on OS should be the most important end point in trials with chemotherapy [27]. Unfortunately, there is no single maintenance trial conducted to date that has reached a sample size with enough power to detect OS improvement.

An exploratory subset analysis, adjusted by stratification factors, showed that maintenance therapy could be of benefit in terms of OS only to patients with lower CA-125 levels (< 10 UI/ml), which seems to be correlated with lower tumor burden and less aggressive prognosis. However, this is merely an exploratory analysis suggesting a possible differential treatment effect in terms of OS between the baseline CA-125 groups.

Health-related quality of life (HR-QOL) in this setting has not been previously analyzed. In the absence of clear evidence for survival advantages, the impact on HR-QOL after long-term treatment with maintenance chemotherapy should be mandatory. Some studies, however, found that the majority of patients with ovarian cancer prefer to be under treatment, even if the oncologic benefits are scarce [28], improving patients' emotional and global HR-QOL [29].

The economic cost of maintenance treatment is ignored as well. Apart from the direct cost of the treatment itself, indirect costs can account for up to 85 % of the total cost [30]. These include loss of work productivity, caregiver time, and other factors.

Another important issue is that maintenance therapy might increase the likelihood of emerging chemoresistant tumor cells, decreasing the possibility of successful treatment at the time of recurrences with platinum chemotherapy. Future studies could elucidate this aspect.

The GOG is currently performing a confirmatory study (GOG 0212) (NCT 00108745) in patients with FIGO stage III–IV epithelial ovarian cancer or primary peritoneal cancer. This is a 3-arm randomized trial comparing observation alone versus 12 months of single-agent paclitaxel versus polyglutamate paclitaxel until documented relapse. The primary end point of the study is OS and the secondary end points will evaluate PFS and HR-QOL. The study is currently accruing patients and the results might probably answer some of the issues under discussion.

Anti-angiogenic Therapy

Angiogenesis is a process by which new microvascular (lymphatic and hematic) networks develop from existing vessels and is orchestrated by a collection of key growth factors involved in both the initiation and maturation phases. These growth factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and angiopoietins. In many solid tumors such as ovarian cancer, angiogenesis is a phenomenon of the tumor microenvironment; promotes tumor proliferation, invasion, and metastasis; and is fundamental to disease progression [31].

As mentioned earlier, for ovarian cancers, the majority of which are high-grade serous adenocarcinomas, genetic instability in tumor cells has been linked with resistance to cytotoxic and other tumor cell-directed therapies. Thus, identifying

a method to "sequester" tumor cells by targeting the tumor microenvironment (relatively genetically stable) might be a useful adjunct, especially in a maintenance setting in patients with cancers at high risk of early progression. Going hand in hand with this concept is the observation that the degree of tumor angiogenesis detected pathologically in tumors and the expression of VEGF, for example, has correlated with malignant behavior [32–34], as well as short PFS and poor OS [35–38], often independent of known prognostic factors.

Pro Angiogenesis

Unlike the case for most non-gynecologic solid tumors, anti-angiogenic agents have demonstrated single-agent activity for patients with recurrent ovarian cancers, in terms of objective responses and PFS. The highest level of evidence for benefit in patients with ovarian cancer is with bevacizumab, a humanized anti-VEGF monoclonal antibody. On the basis of independent phase II trial results [39, 40], for many years, bevacizumab has been listed by the US National Comprehensive Cancer Network as a preferred agent for the management of recurrent ovarian cancer [21]. Results of two positive front-line cooperative group phase III trials were recently reported [41, 42]. Both trials assessed the addition of bevacizumab in combination with standard carboplatin-paclitaxel chemotherapy (6 cycles, every 3 weeks with carboplatin at an AUC of 6 plus paclitaxel at 175 mg/m^2) followed by bevacizumab continued in the absence of disease progression or unacceptable toxicity for a predefined number of cycles every 3 weeks post-chemotherapy in patients who had undergone primary staging/debulking surgery.

GOG 0218 was a placebo-controlled, double-blind trial in 1,873 patients with stage III incompletely debulked or stage IV disease and included a third treatment arm with bevacizumab administered only during the chemotherapy phase [41]. Two-thirds of the patient population had high-risk advanced disease, i.e., stage III cancers with macroscopic residual lesions at least 1 cm in any dimension or stage IV cancers. ICON 7 was an open-label, two-arm study of 1,520 patients with high-risk early stage and with advanced disease [42]. Only approximately one third of the study population had high-risk advanced disease. The primary outcome measure for both trials was PFS. For GOG 0218, the median PFS for patients assigned to chemotherapy alone was 10.3 and 11.2 months for those assigned to chemotherapy plus bevacizumab limited to the chemotherapy phase, and 14.1 months for those assigned to chemotherapy plus bevacizumab during chemotherapy and extended to a maximum of 16 additional cycles. Prolongation of PFS was statistically significant only for the group in which bevacizumab was maintained beyond the chemotherapy phase (HR 0.717, 95 % CI 0.625–0.824) [41]. For ICON 7, a significant improvement in PFS was observed for patients assigned to treatment with chemotherapy plus bevacizumab followed by bevacizumab continued for a maximum of 10 additional cycles, with a median shift from 17.4 months in the control group to 19.8 months in the experimental group (HR 0.87, 95 % CI 0.77–0.99) [42]. One explanation for the relatively modest effect on PFS seen in ICON 7 in comparison to GOG 0218 was the risk level of the population. Consistent with this explanation was a post-hoc analysis of the 465 patients in ICON 7 with high-risk advanced disease, where the improvement in PFS was more substantial, with a median shift from 10.5 months in the control group to 15.9 months in the experimental group (HR 0.68, 95 % CI 0.55–0.85). As mentioned earlier, due to the inability to control for subsequent therapies for a disease with relatively long post-progression survival time, OS can be an unreliable outcome measure, thus justifying PFS as a more pure primary end point [14]. This was especially true for GOG 0218, a trial conducted in regions of the world where bevacizumab (among many subsequent regimens) had been used widely in the management of recurrent disease and for which the HR for death was 0.89 (not statistically significant). For ICON 7, conducted in locations where bevacizumab was relatively inaccessible, the HR for death was 0.85 in the intent-to-treat analysis. However, in the post-hoc subset analysis of those with high-risk advanced disease, a significant OS benefit was observed for the group assigned to treatment containing bevacizumab, with a shift in median OS from 28.8 months for the control group to 36.6 months for the experimental group (HR 0.64, 95 % CI 0.48–0.85).

For both GOG 0218 and ICON 7, the experimental regimens were similarly well tolerated, with the spectrum and severity of adverse events similar to previous phase III trials of metastatic non-gynecologic cancers. For GOG 0218, as an example, while the gastrointestinal perforation and fistula rates in the two bevacizumab cohorts were almost double that seen in the chemotherapy alone group, this complication occurred in less than 3 % overall. Hypertension requiring medical management was observed in up to 23 % and, as expected, was significantly more common in the bevacizumab-treated patients, but only 15 of over 600 patients in the extended bevacizumab cohort required treatment discontinuation based on hypertension. There was no apparent difference in the rates of other adverse events, including febrile neutropenia, thromboembolic events, or wound healing complications. Importantly, as it relates to the maintenance therapy paradigm, the vast majority of adverse effects were observed during the chemotherapy treatment phase [41]. In both trials, formal quality of life assessments showed no significant diminution in quality of life indices associated with extended bevacizumab therapy.

It would appear that the efficacy of anti-angiogenic agents such as bevacizumab is highly dependent on duration. This is completely consistent with notion that angiogenesis is a relatively genetically stable host process which may be controlled but also may be recapitulated in response to growth factors

elaborated by the tumor cell compartment after discontinuation of anti-angiogenic therapy. Indeed, the magnitude of benefit in the GOG 0218 and ICON 7 populations may not have been maximal, as treatment with bevacizumab was continued to a predefined number of cycles in the absence of disease progression or unacceptable adverse effects. In the case of two other recently reported positive phase III trials in the recurrent disease setting, where bevacizumab was continued until disease progression, the magnitude of PFS benefit was more substantial, with an HR of 0.484 for a trial in patients with platinum-sensitive disease [43] and of 0.480 for a trial in patients with platinum-resistant disease [44].

Multiple phase III trials of other anti-angiogenic agents are ongoing. Three of these are examining anti-angiogenic therapy maintained after completion of frontline cytotoxic therapy and involve the angiogenic growth factor tyrosine kinase inhibitors nintedanib [45] and pazopanib [46] and the novel fusion protein AMG-386, which neutralizes primarily the activity of angiopoietin-2 [47].

In summary, based on the justification for PFS as a primary end point in frontline trials, including those involving maintenance therapy, the significant prolongation of PFS demonstrated in several phase III trials, and the absence of new safety signals or impairment of quality of life, the use of anti-angiogenic agents such as bevacizumab should be implemented in part as an extension of standard frontline therapy until at least disease progression in women with advanced stage ovarian cancer.

Con Angiogenesis

Bevacizumab is the most well-studied anti-angiogenic agent. During the late 2000s, several phase I–II trials using bevacizumab have demonstrated its safety and oncologic outcomes in patients with relapsed ovarian cancer [39, 48]. As mentioned previously, in 2011, the results of two large phase III international studies using bevacizumab in first-line/adjuvant chemotherapy were published: GOG 0218 [41] and ICON 7 [42].

Despite both trials having met their primary end point, controversies exist about the use of bevacizumab in the frontline setting as a new standard of treatment for ovarian cancer. The following arguments are often raised, when discussing this controversial issue:

1. PFS is not considered by many opponents a valid end point. For a treatment with a high cost, it would be more convincing a clear advantage on OS. However, there are several reasons why, even with more mature data, a clear survival advantage could not be demonstrated. First, the high crossover rate to bevacizumab in about 30 % of patients in the control arm of GOG 0218 may have decreased the impact on OS potentially achieved in the experimental arm. Second, ovarian cancer is a disease for which a long post-progression survival is expected, in relation to the efficacy of subsequent lines of treatment. From a methodological point of view, the longer the PFS, the higher the number of patients needed to demonstrate an advantage on OS similar to that observed in PFS. In this respect, neither GOG 0218 nor ICON 7 included enough patients to reach this goal, and therefore, it will be very unlikely that these trials will ever demonstrate a benefit in OS.
2. Even when accepting PFS as a valid end point, according to what stated by the 4th Ovarian Cancer Consensus Conference [14], *the magnitude of the effect observed in both GOG 0218 and ICON 7 is less than expected from previous phase II data*. One of the major problems in quantifying the magnitude of the effect is related to the duration of bevacizumab maintenance phase. It appears evident that the size of the effect is not constant over time and decreases after bevacizumab discontinuation. While in GOG 0218 the median PFS crosses the curve at the time of maximal effect, this is not the case for ICON 7 where the largest divergence of PFS curves is seen at 12 months, when bevacizumab was discontinued. This could explain the very small difference in the median PFS observed in ICON7 and why this value may not represent the best way to evaluate the potential benefit. However, this could also mean that the two trial designs cannot completely elucidate the real impact of bevacizumab on PFS, since this drug could have been continued for a longer period of time or until progression. If one accepts this observation, then the results of GOG 0218 and ICON 7 are not conclusive in respect to the magnitude of the benefit in prolonging PFS. An ongoing phase III trial is evaluating the optimal initial treatment duration of bevacizumab in combination with standard chemotherapy in patients with ovarian cancer (BOOST). The study compares bevacizumab as maintenance therapy for 15 versus 30 months [49].
3. Besides the modest PFS benefit, toxicity, inconvenience for both the patient and her family, and cost should be considered. When looking at the toxicity profile in both studies, even though grade 2 or more hypertension was the only significant adverse event when bevacizumab was used, an increasing trend of other adverse events when implemented as maintenance therapy was noted. These include grade 2 or more gastrointestinal events, grade 3 or more proteinuria, venous and arterial thromboembolism, grade 3 or more bleeding, and reversible posterior leukoencephalopathy. It is interesting to note, however, that the majority of the toxic events occurred during primary chemotherapy and within the perioperative period.

   The potential cost-effectiveness analysis of adding bevacizumab to first-line treatment of advanced epithelial ovarian cancer was addressed as well [50]. One study analyzed the GOG 0218 trial using a simplified cost-effectiveness

analysis. They estimated the drug costs using US Medicare reimbursement rates. This model, however, did not include the additional cost of the maintenance treatment, such as loss of work productivity, hospital out-of-pocket expenses, and travel/hotel expenses. In addition, the only cost of toxicity included was bowel perforation management. The analysis demonstrated that bevacizumab used in maintenance therapy has an incremental cost-effectiveness ratio of US$ 1,305,000 per patient and a total of US$ 401,088 per year of PFS. The study also estimates that the drug would be cost-effective if 32.1 months of PFS could be achieved. On the other hand, the study calculates that the cost of the drug should be reduced to 25 % of the current cost for it to be cost-effective. The authors concluded that the addition of bevacizumab to standard chemotherapy in patients with advanced ovarian cancer is not cost-effective [50]. An expected reduction of its price might improve the cost-effectiveness ratio, helping its incorporation into clinical practice in frontline treatment. The ICON-7 used half of the dose for a shorter duration with similar oncologic outcomes; thus, an additional reduction in the cost could be achieved by using this administration scheme.

4. Patient selection. From a subset analysis performed in the ICON 7 population, the maximum benefit was seen in patients with more extensive disease after surgical cytoreduction. An updated analysis of a subset of 465 high-risk patients with more extensive disease in the ICON-7 showed 7.8 months' improvement in the OS with a hazard ratio of 0.64 (95 % confidence interval, 0.48–0.85) [51]. Thus, bevacizumab might not be equally effective in all women, and a better patient selection should be identified in the future. Further controversies were raised after the advantage of bevacizumab in prolonging PFS was also demonstrated in patients with recurrent ovarian cancer: the OCEANS study showed an improvement in PFS of 4 months in patients with platinum-sensitive recurrent ovarian cancer [43], while the Aurelia study demonstrated a 3.4 increase in PFS in a population of platinum-resistant recurrent ovarian cancer [44]. Based on these data, some authors suggested that the use of bevacizumab would be more cost-effective in second line, where a greater benefit may be achieved in a population at higher risk for further relapse. Ongoing biomarker studies in both GOG 0218 and ICON 7 studies will better clarify the issue of patient selection.

Other phase III trials using anti-angiogenic therapy as maintenance treatment in first-line recently completed their accrual. The LUME-Ovar 1 study is a pharmaceutical sponsored, multicenter, randomized, double-blind phase III trial to investigate the efficacy and safety of BIBF 1120 (nintedanib) in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in patients with advanced ovarian cancer [45]. Nintedanib is a multi-target angiokinase inhibitor, which blocks VEGFR, platelet-derived growth factor receptors (PDGFR), and fibroblast growth factor receptors (FGFR). Another phase III trial evaluated the efficacy and safety of 24 months' maintenance with pazopanib monotherapy versus placebo after first-line chemotherapy [46]. Pazopanib is a multi-tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α and PDGFR-β, FGFR-1 and FGFR-3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). Finally trebananib (also referred as AMG 386) is a peptide-Fc fusion protein that neutralizes the interaction between the Tie2 receptor and angiopoietin-1/2. It is currently being evaluated in the adjuvant setting, concomitant with standard chemotherapy followed by a maintenance period [47].

In summary, despite evidence of efficacy for anti-angiogenic therapy observed in well-designed large clinical studies, several questions remain unanswered regarding optimal dose and duration of treatment, cost, toxicity, impact on quality of life, and selection of patients likely to benefit.

Conclusions

Given the unacceptably high relapse rate ultimately leading to cancer specific death, there appears to be a rationale to extend antineoplastic therapy for advanced ovarian cancer beyond the completion of standard primary treatment. The proof of principle justifying this approach has to this point been demonstrated for maintenance taxane and anti-VEGF therapy but only with respect to prolongation of progression-free survival. Due to the availability of multiple effective regimens in the management of recurrent disease, including reuse of taxanes and anti-angiogenic drugs, coupled with long relative initial post-progression survival times, the designs of previously "positive" frontline trials have been limited in their ability to detect a favorable and meaningful effect on overall survival, even if one exists. Furthermore, the impact with respect to adverse effects, quality of life, and health-care costs must be considered in the balance. The application of these modalities in the clinical management of patients with advanced ovarian cancer must be individualized, with careful counseling related to potential benefits and risks.

Future Directions

It would appear that the major goal of maintenance therapy for advanced ovarian cancer would be to improve long-term outcomes, including prolonging length of survival with acceptable quality of life or increasing the proportion of patients ultimately cured. In this regard, continued investigation is needed along two lines – (1) optimizing the approaches already established to provide some evidence of benefit and (2) developing alternative

novel strategies. For example, it has become evident that increasing the frequency of taxane administration at lower doses can provide improvements in efficacy compared to standard dose and schedule during frontline therapy [18]. This strategy could potentially be investigated in the maintenance setting for its potential to provide an improved therapeutic index. For bevacizumab, based on the subset analysis of ICON7 [42] and data from randomized trials in second-line therapy [43, 44], it may be that maintaining therapy in patients with macroscopic residual tumor at the completion of cytoreductive surgery until at least disease progression compared to a predefined time point would be more rational and consistent with mechanism of action. Recently, a phase III trial in patients with metastatic colorectal cancer demonstrated an improvement in overall survival for bevacizumab continued beyond disease progression in the context of second-line chemotherapy after a primary regimen containing bevacizumab [52]. Still another approach might be to investigate the combination of high-frequency low-dose paclitaxel in combination with bevacizumab or another anti-angiogenic agent in the maintenance setting.

With regard to novel methods, given the high-frequency of homologous recombination repair defects, particularly in high-grade serous adenocarcinomas, the use of poly (ADP-ribose) polymerase (PARP) inhibitors could be considered in the maintenance setting following first-line therapy. Recently, two randomized trials of the oral agent olaparib demonstrated significant prolongation in progression-free survival in the recurrent disease setting when used purely in maintenance following prior platinum-based chemotherapy [53] or in the context of platinum-based chemotherapy followed by maintenance with olaparib [54]. In addition, the maintenance setting would seem to be ideal for the implementation of immunotherapeutics. Unfortunately, controlled trials thus far have failed to demonstrate benefit [25, 55]. An explanation for their shortcomings has been the failure to combine appropriate antigen selection, enhanced antigen presentation, and modulation of host effector cell function. Certainly, the realm of molecular therapies targeting specific mechanisms of disease progression is still in its infancy with respect to advanced ovarian cancer and could theoretically be applied to maintenance therapy of the future. Their success, however, will depend on clinical trial designs that incorporate selection/stratification based on established parameters which would predict benefit based on tumor or host biology.

Concluding Comments

- Despite encouraging results, neither chemotherapy nor anti-VEGF therapy has reached the major goal of improving long-term outcomes and cure rate of patients with advanced ovarian cancer. Continued investigation is needed to optimize the use of anti-VEGF therapy in respect to patient selection, optimal dose, optimal duration, adverse effects, quality of life, and health-care costs.
- Future investigations should include the search for alternative novel strategies to be used in combination with or in substitution to anti-VEGF therapy. Among them, compounds targeting different angiogenic pathways are currently under investigation, while the use of poly (ADP)-ribose polymerase (PARP) inhibitors could be considered in the maintenance setting of high-grade serous adenocarcinomas.
- *The ultimate goal would be to* predict benefit based on tumor or host biology, in order to select the most effective and possibly less toxic treatment for each individual. In order to reach this objective, future clinical trial designs must incorporate selection/stratification criteria based on established parameters.
- *The implementation of a more personalized approach should hopefully lead to* improving long-term outcomes, prolonging length of survival with acceptable quality of life, and increasing the proportion of patients ultimately cured.

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What Is the Value of Lymphadenectomy in Early Ovarian Cancer?

16

Sven Mahner, Jacobus Pfisterer,
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Summary Points

- Is a full systematic lymphadenectomy always better than lymph node sampling alone?
- Can lymph node assessment be safely avoided in certain subtypes of ovarian cancer?
- Can the prognosis be improved with lymphadenectomy?
- What important unanswered questions can be addressed by appropriately designed clinical trials?

Introduction

As the role of lymphadenectomy is controversial, we designed this chapter in a pro and con fashion. The authors of the first part, Sven Mahner and Jacobus Pfisterer, argue for a systematic lymphadenectomy in all cases of apparent early-stage ovarian cancer and lay out the evidence to support their recommendation. Then Ganendra Raj Ali Mohan and Michael Quinn, the authors of the second part, argue against this approach. Finally, all four authors try to reach a consensus as a basis for routine practice in this clinical situation.

Pro Lymphadenectomy

S. Mahner and J. Pfisterer

A quarter of all patients with ovarian cancer will be diagnosed in early stages [1]. Traditionally, the International Federation of Gynecology and Obstetrics (FIGO) Stages IA–IIA are referred to as "early" stage, having an excellent 10-year survival rate of more than 80 % [2]. In contrast, the 5-year survival rate of advanced stage ovarian cancer FIGO-stages IIB-IV ranges between 30 and 50 % [3].

Staging recommendations implemented a surgical staging algorithm that includes pelvic and para-aortic lymph node sampling or lymphadenectomy in 1988. Almost 25 years later, many women with presumed early-stage ovarian cancer are still inadequately staged [4]. Lymph node assessment is among the most frequently omitted steps of comprehensive staging [5], even though women with presumed early-stage disease are often upstaged by thorough staging [6, 7] and up to 30 % of patients with "clinical early-stage" disease will have positive lymph nodes resulting in Stage III classification [8–24].

The systematic assessment of pelvic and para-aortic lymph nodes as an integral part of complete surgical staging in apparently early-stage ovarian cancer is also reflected in European and American guidelines [25, 26]. It

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comprises resection of the para-aortic, paracaval, and inter-aorto-caval lymph nodes up to the renal vessels as well as the pelvic lymph nodes along the common iliac, external and internal iliac vessels, and the obturator fossa. Even if macroscopic tumor involvement appears to be unilateral, it is important to perform a complete bilateral resection, as a substantial proportion will have bilateral lymph node metastases [27]. The procedure requires special surgical expertise and experience, as significant morbidity can occur even with well-trained surgeons. As surgery takes place along the large retroperitoneal vessels, vascular injury with subsequent hemorrhage or thromboembolic complications might occur as well as adhesions, ileus, or injury to the ureter or small and large bowel [28]. Most frequent long-term complications include lymphocysts, lymphatic ascites, or lymphedema. Despite defined areas of dissection, there is to date no agreed definition of "adequate" lymph node dissection, and the number of resected nodes is a surrogate at best. Nodal counts may depend on various factors besides surgical expertise such as anatomical variations among patients and the comprehensiveness of pathologic analysis.

An adequate staging procedure will enable the gynecologic oncologist to apply appropriate adjuvant treatment by providing a secure diagnosis. Furthermore, thorough lymphadenectomy may even improve survival by removing metastatic disease within the lymph nodes and preventing otherwise incomplete tumor "debulking" [29].

But What Is the Evidence for the Value of Lymphadenectomy in Early Ovarian Cancer?

We have clear evidence that complete staging is of prognostic significance [2, 30, 31]. As lymphadenectomy is a crucial part of surgical staging [32], it might be an important prognostic factor itself.

The randomized Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) evaluated adjuvant chemotherapy in 448 patients with early-stage ovarian cancer [30]. In a subset analysis of this trial analyzing only patients without adjuvant chemotherapy, it was shown that lymphadenectomy as part of the surgical management was directly related to disease-free survival (DFS) and overall survival (OS) [33]. Five-year OS decreased from 89 % in optimally staged patients to 71 % in patients without lymph node assessment ($p=0.01$); 5-year DFS decreased from 79 to 61 %, respectively ($p=0.03$). The same was observed in a large retrospective analysis of 6,686 patients with Stage I ovarian cancer from the Surveillance, Epidemiology and End Results (SEER) program [34] in which 42.8 % of the patients received lymph node assessment as part of their staging, and in this group disease-specific survival was improved from 87 to 92.6 % ($p<0.001$). The prognostic relevance of the extent of lymph node dissection (0 resected nodes vs. 1–10 nodes vs. >10 nodes) was also analyzed and showed a significant increase of 5-year disease-specific survival from 87 to 91.9 % to 93.8 %, respectively ($p<0.001$). Of note, the effect of the extent of lymph node staging remained an independent prognostic factor also in multivariate analysis.

The positive prognostic effect of surgical comprehensiveness in retroperitoneal lymph node resection was observed in other series, too [35], and it isn't surprising that the likelihood of detecting lymph node metastasis increases substantially with the number of removed nodes [36] and assessment of all relevant regions [37].

There is also one randomized trial comparing complete, radical, systematic lymphadenectomy (138 patients) to lymph node sampling (130 patients) in early ovarian cancer [15]. In this trial, the median number of removed nodes was 47 in the systematic group and 5.5 in the sampling group ($p<0.001$). Operating time was 90 min longer in the lymphadenectomy group (240 vs. 150 min, $p<0.001$), but the incidence of postoperative complications was similar. A significantly higher amount of 22 % patients had lymph node metastasis in the systematic group compared to 9 % in the sampling group ($p=0.007$). The trial had insufficient statistical power to demonstrate differences in the DFS or OS. Nevertheless, a trend towards improved outcome for thoroughly staged patients was observed with a 5-year DFS of 78.3 % versus 71.3 % (HR 0.72; 95 % CI 0.46–1.21, $p=0.16$) and 5-year OS of 84.2 % versus 81.3 % (HR 0.85, 95 % CI 0.49–1.47, $p=0.56$). Besides the lack of adequate power to detect survival differences, there was a significant imbalance between the two arms in terms of adjuvant chemotherapy. Significantly more node-negative patients in the sampling arm (66 %) received adjuvant treatment compared to the complete lymphadenectomy arm (51 %, $p=0.03$), and given the well-known effect of adjuvant treatment in inadequately staged ovarian cancer patients [2], this imbalance might have affected the detection of a survival difference.

What Are the Possible Consequences of a Systematic Lymphadenectomy?

A consequence of a lymphadenectomy in early-stage ovarian cancer is confirmation that a patient has a true FIGO Stage IA and may therefore in the absence of other risk factors avoid adjuvant chemotherapy. However, a patient with presumed early ovarian cancer and positive lymph nodes will be upstaged to FIGO stage IIIC as suggested. This has prognostic significance, but the key question is whether removal of these nodes, so reducing tumor bulk, will lead to an improvement in prognosis following chemotherapy due to the absence of residual tumor.

Conclusion

Retroperitoneal lymph node dissection plays an important role in the management of early ovarian cancer. It is an integral component of surgical staging, and there is no doubt that accurate surgical staging has a major impact on survival. There is no level 1 evidence that systematic lymph node dissection itself improves survival in patients with early-stage ovarian cancer, but it would be difficult to conduct a randomized trial of lymphadenectomy versus no lymphadenectomy in early-stage disease.

Therefore, all patients with apparently early-stage ovarian cancer should undergo systematic pelvic and para-aortic lymphadenectomy performed by an experienced gynecologic oncologist.

Lymphadenectomy in Early Ovarian Cancer: Too Many Unanswered Questions to Recommend It as Routine

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Approximately 30 % of patients presenting with early-stage ovarian cancer will have their cancers upstaged after more extensive surgery [6]. Up to 22 % of these will be upstaged mainly because of positive retroperitoneal nodes [38]. It is unclear how many patients have positive nodes detected from routine lymphadenectomy and how many from sampling of suspicious nodes, so in other words, only 6–7 % of women at most may benefit from removal of lymph nodes, and this assumes that removal of positive microscopic and macroscopic nodes may increase cure rates, either due to the surgery itself or due to cytotoxic chemotherapy which may never have otherwise been given. Recent evidence suggests that the prognosis of patients with advanced ovarian cancer is improved when they are left with no macroscopic intra-abdominal disease after surgery, irrespective of the retroperitoneal nodal status [39]. With the emergence of this new evidence from the surgical management of patients with advanced ovarian cancer, it is only appropriate that we review the role of lymphadenectomy in the management of patients with early-stage ovarian cancer.

What Is the Extent of Lymphadenectomy Required in Patients Presenting with Early-Stage Ovarian Cancer?

The type of lymphadenectomy performed for patients with early-stage ovarian cancer varies among published studies. The three most common ways to perform a lymphadenectomy so far described consist of removal of enlarged palpable nodes, sampling of the pelvic and para-aortic lymph nodes, and performing a radical systematic pelvic and para-aortic lymphadenectomy up to the renal veins bilaterally. There have also been extensive discussions whether a unilateral or bilateral pelvic and para-aortic lymphadenectomy be performed in unilateral primary disease. Benedetti-Panici et al., for instance, suggested a unilateral lymphadenectomy is sufficient for patients presenting with unilateral ovarian tumors, while others disagree since the presence of bilateral metastasis in the retroperitoneal areas even when the tumor is confined to one ovary has been demonstrated (Table 16.1) [9, 19]. Sampling of lymph nodes from the pelvic and para-aortic areas results in a smaller number of lymph nodes harvested when compared to systematic lymphadenectomy. In one study [36], the average number of lymph nodes removed was 10 (range from 1 to 37) with a median number of 8 compared to other studies where radical pelvic and para-aortic lymphadenectomy was performed with counts which vary from 40 to 49 [36, 40, 41]. The range for sampling is notable and immediately alerts the reader to the inexactitude of this approach.

Onda et al. performed a retrospective review of patients who underwent systematic lymphadenectomy and suggested that if sampling only was performed, then a group of patients with micrometastatic disease in the retroperitoneal area will be missed [37]. They also reported on two specific areas (potentially sentinel areas) in the pelvic and para-aortic region that gave the highest sensitivity value for positive lymph node detection for all stages. They suggested that if sampling only is to be performed, then these are the areas which should be sampled.

From the study of Onda et al. and others in the literature, it has become clear that the distribution of metastatic disease in these patients is hard to predict, and the only way to correctly identify these microscopic deposits is therefore by performing a systematic lymphadenectomy. A radical systematic pelvic and para-aortic lymphadenectomy entails removal of lymph nodes from different anatomical regions in the pelvic and para-aortic areas in a systematic fashion. The para-aortic and the paracaval regions between the renal veins and the inferior mesenteric artery are the most important regions. The other areas included in this procedure are the common iliac, internal iliac, external iliac, and the obturator fossa. Complications can occur while performing a systematic lymphadenectomy, of which severe hemorrhage intraoperatively can be life-threatening [28]. Based on the reported incidence from published studies, the rate of complications is higher when performing a systematic lymphadenectomy compared to debulking enlarged nodes or when sampling only is performed. In the only randomized study comparing systematic lymphadenectomy to sampling, there was a significant impact on the median operative times, amount of blood loss, proportions of patient undergoing blood transfusions, and median hospital stay [42]. Other serious complications that can occur are injuries to the small and large bowel and ureteric injuries. Postoperative complications

Table 16.1 Overall incidence of lymph node metastases in clinical FIGO Stage I–II epithelial ovarian cancer and the anatomical distribution of positive lymph nodes

	Clinical FIGO	Positive pelvic and para-aortic lymph nodes										
		Overall		Only para-aortic (PA)			Only pelvis (P)			Both para-aortic and pelvic		
Reference	Stages I–II	*n*	*a*%	*n*	*b*%	*a*%	*n*	*b*%	*a*%	*n*	*b*%	*a*%
Ayahan et al.	169	11	6.5	5	45.5	3.0	6	54.5	3.6	0	0.0	0.0
Benedetti et al.	37	5	13.5	2	40.0	5.4	3	60.0	8.1	0	0.0	0.0
Burgardt et al.	27	8	29.6	1	12.5	3.7	3	37.5	11.1	4	50.0	14.8
Desteli et al.	33	2	6.1	1	50.0	3.0	1	50.0	3.0	0	0.0	0.0
Fournier et al.	108	19	17.6	10	52.6	9.3	5	26.3	4.6	4	21.1	3.7
Harter et al.	70	8	11.6	4	50.0	5.8	0	0.0	0.0	4	50.0	5.8
Morice et al.	100	23	23.0	13	56.5	13.0	3	13.0	3.0	7	30.4	7.0
Negeshi et al.	150	19	12.7	14	73.7	9.3	2	10.5	1.3	3	15.8	2.0
Nomura et al.	79	10	12.7	4	40.0	5.1	1	10.0	1.3	5	50.0	6.3
Onda et al.	59	13	22.0	2	15.4	3.4	3	23.1	5.1	8	61.5	13.6
Saguraki et al.	94	9	9.6	7	77.8	7.4	1	11.1	1.1	1	11.1	1.1
Suzuki et al.	47	5	10.6	2	40.0	4.3	2	40.0	4.3	1	20.0	2.1
Takeshima et al.	193	38	19.7	17	44.7	8.8	6	15.8	3.1	15	39.5	7.8
Tsumara et al.	81	7	8.6	6	85.7	7.4	0	0.0	0.0	1	14.3	1.2
Total	**1,247**	**177**	**14.2**	**88**	**49.7**	**7.1**	**36**	**20.3**	**2.9**	**53**	**29.9**	**4.3**

Taken from Kleppe et al. [44]. Review with permission from Elsevier
FIGO International Federation of Gynecology and Obstetrics
a%: The percentage indicates the number of patients with positive lymph nodes as a proportion of the total number of patients with clinical FIGO Stage I–II tumors
b%: The percentage indicates the number of patients with positive lymph nodes in that particular anatomical region as a proportion of the patients with positive lymph nodes

such as infection, ileus, pulmonary embolism, lymphocyst formation, and lymphedema are also common problems seen in these patients. If these patients are upstaged and needing adjuvant chemotherapy, some of these complications can potentially delay their treatment. Before proceeding with a radical systematic pelvic and para-aortic lymphadenectomy with its inherent risks, therefore, one has to consider the small marginal benefit in a limited number of patients especially given the not inconsiderable late toxicity (which has never been described).

Treating a select group of patients with high-risk features independent of lymph node status therefore seems rational and reasonable especially as many of those patients with positive nodes will be upstaged anyway with other sites of detected metastatic disease such as positive cytology or microscopic omental disease [30, 43].

Are There Any Identifiable High-Risk Features in Apparent Early-Stage Disease That Increase the Likelihood of Having Positive Retroperitoneal Lymph Nodes?

Kleppe and co-researchers from the Netherlands undertook a systematic review of the literature on the incidence of nodal metastasis in patients with early-stage ovarian cancer (Stages I and II) with reference to the grade and histology of the presenting ovarian tumor [45]. The mean incidence of nodal metastasis in patients with clinical Stage I to II ovarian cancer was 14.2 % (ranging from 6.1 to 29.6 %), of which 7.1 % were present only in the para-aortic region, 2.9 % only in the pelvic region, and 4.3 % both in the pelvic and para-aortic regions. Based on the grading of ovarian tumor, the incidence of nodal metastasis was only 4 % in patients with Grade 1 tumors, 16.5 % in patients with Grade 2 tumors, and 20 % in patients with Grade 3 tumors. However, when the incidence was limited to only patients with clinical Stage I disease, the incidence of lymph node metastasis in Grade 1, 2, and 3 tumors was 2.9, 13.8, and 20 %, respectively (Tables 16.1 and 16.2). The incidence of lymph node metastasis also differed according to the histology of the tumor being highest in patients with serous epithelial ovarian cancers (19.3 %) compared to mucinous tumors which had the lowest incidence (1.9 %) (Table 16.3). A recent publication from Japan has suggested that patients with Stage I A clear cell cancers of the ovary could be treated conservatively in the same way as other favorable histologies [46].

Based on the data presented in this systematic review, we could make an argument for not performing lymphadenectomy in patients with Stage 1A Grade 1 tumors and in patients with early-stage mucinous ovarian cancers as the risk of nodal metastasis appears to be very low. The incidence of node positivity in this group of patients with Stage 1A Grade 1 disease with favorable histology probably lies between 2.9 and 4 % [45]. Closely following up these patients with a PET/CT after 6 and 12 months after surgery may be a reasonable option as there is evidence that isolated recurrences in the retroperitoneal area in this group of patients can be excised with good prognosis [47, 48].

Table 16.2 Incidence of lymph node metastases in clinical Stages I–II according to differentiation grade

	Total population	Grade 1			Grade 2			Grade 3			Missing data
Reference	*n*	Total/*n*	LN+/*n*	*a %*	Total/*n*	LN+/*n*	*a %*	Total/*n*	LN+/*n*	*a %*	*n*
Desteli et al.	33	11	0	0.0	8	0	0.0	14	2	14.3	
Harter et al.	48	10	0	0.0	25	2	8.0	13	1	7.7	
Morice et al.	60	15	0	0.0	21	4	19.0	4	4	100.0	20
Nomura et al.	79	21	1	4.8	13	3	23.1	6	2	33.3	39
Sakuragi et al.	94	60	3	5.0	25	5	20.0	9	1	11.1	
Suzuki et al.	47	32	2	6.3	11	3	27.3	4	0	0.0	
Total	**361**	**149**	**6**	**4.0**	**103**	**17**	**16.5**	**50**	**10**	**20.0**	**66**

Taken from Kleppe et al. [44]. Review with permission from Elsevier
LN+: Lymph node metastases
a %: The percentage indicates the number of patients with positive lymph nodes in the mentioned grade as a proportion of the total number of patients of that grade

Table 16.3 Incidence of lymph node metastases according to histological subtype

	Total patients	FIGO Stage	Serous		Mucinous		Endometrioid		Clear cell		Undifferentiated/others	
Reference	*n*		LN+/*n*	*n %*	LN+/*n*	*n %*	LN+/*n*	*n %*	LN+/*n*	*n %*	LN+/*n*	*n %*
Desteli et al.	33	I	1/7	14.2	0/8	0.0	0/5	0.0	0/4	0.0	1/9	11.1
Harter et al.	48	I	2/13	15.4	0/8	0.0	1/14	7.1	0/7	0.0	0/6	0.0
Morice et al.	85	I	8/26	30.8	0/20	0.0	0/25	0.0	–	–	9/14	64.3
Negeshi et al.	150	I–II	5/35	14.3	2/49	4.1	3/15	20.0	8/46	17.4	1/5	20.0
Nomura et al.	79	I–II	6/12	50.0	0/4	0.0	2/27	7.4	2/36	5.6	–	–
Onda et al.	59	I–II	7/21	33.3	1/15	6.7	0/3	0.0	5/16	31.3	0/4	0.0
Suzuki et al.	47	I	4/13	30.8	0/22	0.0	0/3	0.0	1/9	11.1	0	0.0
Tsumura et al.	73	I–II	2/23	8.7	1/29	3.4	–	–	4/21	19.0	–	–
Total	**574**		**35/150**	**23.3**	**4/155**	**2.6**	**6/92**	**6.5**	**20/139**	**14.4**	**11/38**	**28.9**

Taken from Kleppe et al. [44]. Review with permission from Elsevier
LN+: Lymph node metastasis
LN+/*n*: Lymph node metastasis/total patient
FIGO International Federation of Gynecology and Obstetrics
n %: The percentage indicates the number of patients with positive lymph nodes in the mentioned histological type as a proportion of the total number of patients in that histologic type

If a systematic lymph node sampling is performed of non-enlarged nodes even when chemotherapy will be given for other reasons such as grade of tumor, then the only rationale for such an approach is to determine the number of chemotherapy cycles these patients should receive (3 vs. 6 cycles; GOG 157) [49]. The Gynecologic Oncology Group study, however, showed that 6 cycles were more effective, and so if we are going to treat patients with serous tumors (which is the most common histology seen in our practice) using 6 cycles of chemotherapy anyway, then it reasonable to believe that microscopic deposits in the retroperitoneal area will be eradicated with this treatment and formal removal is unnecessary [50].

Which Patients with Early-Stage Ovarian Cancer Might Benefit from a Lymphadenectomy and Does It Improve Survival?

It has been difficult to prove that lymphadenectomy in this group of patients adds any benefit in terms of improving overall survival as the type of lymphadenectomy performed has varied between published studies. In contrast, lymphadenectomy has been shown to be of prognostic significance by identifying a group of patients who have their tumors upstaged to Stage IIIC on the basis of positive retroperitoneal nodes. The only current valid indication for performing a systematic lymphadenectomy is to identify a small group of patients with early-stage ovarian cancer (Stages 1A, IB and Grades 1, 2) who could potentially avoid adjuvant chemotherapy [51]. The GOG conducted a randomized prospective trial in 81 patients with moderately or well-differentiated cancers confined to the ovaries (Stages IA and IB); patients were assigned to receive either no chemotherapy or melphalan (0.2 mg/kg of body weight per day for 5 days repeated every 4–6 weeks for up to 12 cycles). After a median follow-up of more than 6 years, there was no significant difference between the patients given no chemotherapy and those treated with melphalan with respect to either 5-year disease-free survival (91 vs. 98 %; $p = 0.41$) or overall survival (94 vs. 98 %; $p = 0.43$) [51].

The only randomized control study comparing systematic lymphadenectomy with lymph node sampling in patients with early-stage epithelial ovarian cancer macroscopically confined to the pelvis suggested an improvement in the progression-free survival in the group of patients that underwent systematic lymphadenectomy, but there was no improvement in the overall survival [42]. Furthermore, there were no quality of life data available from this study. Indeed, the authors stated that there was a paucity of evidence as to whether or not patients with early-stage disease (Stages I and IIA) should be treated with adjuvant chemotherapy. The results from the ICON 1 and ACTION trial were not yet available at that time.

Since the publication of the ACTION and ICON 1 trial results, patients who are diagnosed with pelvic disease intraoperatively or postoperatively will go on to receive adjuvant chemotherapy which has been proven beneficial in terms of improving their overall survival [30, 43]. Therefore, it would be safe to assume that most gynecological oncologists would not undertake a systematic lymphadenectomy in these patients but instead proceed to excise enlarged nodes in the retroperitoneal area as part of a debulking procedure after satisfactorily removing all their diseases in the pelvis. Performing a systematic lymphadenectomy in these patients would only increase the morbidity of the procedure and not add any real survival advantage. This is further evidenced by a recent meta-analysis in which there was no significant statistical difference in overall survival in patients with early-stage ovarian cancer who had systematic lymphadenectomy in comparison to those that did not [51].

What Other Factors Can Influence the Outcome of Patients with Retroperitoneal Microscopic Disease?

It is important to ensure that proceeding to a systematic lymphadenectomy procedure on top of a long debulking procedure actually translates into better outcomes without substantially increasing the morbidity of the surgery. There is now evidence to suggest that tumors which are upstaged to Stage IIIC disease from Stage I/II disease based on lymph nodes positivity have a much better prognosis than those diagnosed as Stage IIIC including extensive peritoneal disease [52]. An analysis of patients diagnosed with Stage IIIC disease from the Gynecology Oncology Group 182 study [39] compared outcomes of patients diagnosed as Stage IIIC disease by dividing them into three groups based on the amount of disease found intraperitoneally along with the findings of the lymph nodes after lymphadenectomy. Three groups of patients, those with Stage IIIC disease who had less than 2 cm intraperitoneal spread and positive retroperitoneal nodes (the RP group), those with more than 2 cm intraperitoneal disease but negative retroperitoneal nodes (IP, RP–), and those with more than 2 cm intraperitoneal disease with positive retroperitoneal nodes (IP, RP+), were compared. A fourth group of patients who had intraperitoneal disease with less than 2 cm outside of the pelvis and did not have surgical lymph node assessment (IP/RP (?) group) was excluded from the primary analysis but was staged as Stages IIIA and IIIB (Table 16.4). Multivariate analysis revealed that the IP/RP+ group had a worse progression-free survival compared with the RP group. The IP/RP– group also had significantly worse progression-free survival and a trend towards worse overall survival when compared to the RP group. The IP/RP+ and IP/RP– groups had a worse median progression-free survival (PFS), 21 and 29 months, respectively, compared to 48 months in the RP group. The median overall survival (OS) was 63 and 79 months in the IP/RP+ and IP/RP– groups but was not yet reached in the RP group at the time of publication.

Table 16.4 GOG 182 analysis

GOG 182 analysis	PFS (months)	Overall survival
IP/RP+		
More than 2 cm intraperitoneal disease that had positive retroperitoneal nodes after lymphadenectomy	21	63 months
IP/RP–		
More than 2 cm intraperitoneal disease but had negative retroperitoneal nodes on lymphadenectomy (IP, RP–)	29	79 months
RP		
Less than 2 cm intraperitoneal spread and positive retroperitoneal nodes after lymphadenectomy	48	Not yet reached
IP/RP?		
Less than 2 cm outside of the pelvis and did not have surgical lymph node assessment		
73 (9.5 %) of these patients had Stage IIIA disease	34	Not yet reached
94 (12.2 %) had Stage IIIB disease	63	Not yet reached

When a comparison was made between the RP group and the patients classified as Stages IIIA and IIIB who did not have any surgical lymph node assessment (IP/RP (?) group), 9.5 % had Stage IIIA disease because of microscopic tumor deposits outside of the pelvis, and 12.2 % had Stage IIIB disease. These groups of patients had similar PFS (median time to recurrence 34 and 63 months vs. 48 months, respectively, $p=0.2297$), and the median OS was not yet reached yet in all 3 groups. The 5-year OS rate was 50.4, 59.2, and 50.7 % in Stage IIIA, IIIB, and RP groups, respectively. So intraperitoneal disease seems more important in terms of

survival, and indeed the removal of normal lymph nodes may actually have a deleterious effect, presumably on the immune system.

Is There a Better Way to Identify and Manage This Group of Patients Who Will Benefit from Diagnosing Microscopic Disease in the Retroperitoneal Nodes?

Most patients with early disease are referred to the gynecology oncologist after their primary surgery performed either by a general gynecologist or a surgeon. A retrospective study to determine the outcomes of women treated with chemotherapy for clinically apparent early-stage ovarian cancer stratified patients according to whether a staging procedure was performed or not [53] and found that there was no additional benefit from a repeat surgical staging.

The use of sentinel node biopsy in the management of patients with gynecological cancers is being extensively studied [54]. A recent study has examined the feasibility of performing sentinel node biopsy in patients with ovarian cancer [55]. This approach is in its infancy and merits further attention.

The question of whether we can predict the likelihood of para-aortic nodes being positive intraoperatively using frozen section has also been studied [16]. A retrospective analysis on all patients with epithelial ovarian cancer who had a systemic pelvic and para-aortic lymphadenectomy during primary cytoreductive surgery reported that frozen section could not satisfactorily predict which patients would have positive para-aortic nodes. Furthermore, using the pelvic nodes as a predictor of para-aortic lymph node positivity showed a sensitivity of only 50 % in early ovarian cancer and 73 % in the more advanced disease.

A recent report on 12 patients upstaged on final histopathology out of 33 patients with apparent clinical Stage 1A disease [19] included 7 who were upstaged because of the findings of ovarian capsular invasion, another 2 who had contralateral ovarian capsular invasion, while 1 patient had both microscopic omentum deposits with ovarian capsular invasion. Only 2 patients were upstaged because of nodal disease alone. In this series, there were 4 patients with clear cell cancer of the ovary, and as discussed, this is still considered as a high-grade tumor, and in many centers, adjuvant chemotherapy would have been given after surgery for apparent clinical Stage I disease, particularly if there were other adverse features. The 10 patients from the 33 eligible patients who had histological findings of capsular invasion and omental metastasis in this series could have potentially avoided the morbidity of a full lymphadenectomy if this was performed as a two-stage procedure. Most centers would have treated these 10 patients with adjuvant chemotherapy just based on their final histopathology after the operation even if a lymphadenectomy performed was negative for tumor.

Conclusion

Not all patients presenting with early-stage ovarian cancer benefit from a systematic pelvic and para-aortic lymphadenectomy. Whether there is a survival benefit in performing a systematic lymphadenectomy in these patients still remains controversial and unproven. When performing a radical systematic pelvic and para-aortic lymphadenectomy in patients with early-stage ovarian cancer, there is clear evidence from published studies that there will be more normal lymph nodes compared to diseased nodes removed. What we don't know is whether identifying and removing these microscopic positive nodes influences outcomes in a patient population, the majority of whom will receive adjuvant cytotoxic chemotherapy anyway.

Some patients who are suspected to have early-stage (Stages IA, IB and Grades 1, 2) disease might benefit from a two-stage surgical procedure until a less invasive way is found such as sentinel node biopsy or improved sensitivity of PET scanning. Patients in this situation should be counselled and given the option of choosing whether they would prefer to undergo formal staging which requires an extensive surgical dissection of the retroperitoneal area or choose to receive adjuvant chemotherapy. For women who choose not to have a formal staging done, adjuvant chemotherapy has been shown to be beneficial based on a subgroup analysis of unstaged patients in the ACTION trial [30]. If a lymphadenectomy is planned, then it should preferably be performed using minimally invasive surgery [56].

Agreed Position

All authors agree that when lymphadenectomy is undertaken, then a bilateral procedure is necessary. They also agree that there is a need for long-term morbidity and quality of life studies. They failed to reach agreement on whether nodes should be removed in mucinous tumors or whether there was value in removing non-enlarged nodes when enlarged positive nodes had been removed and whether non-enlarged nodes should be removed when other high-risk features are present which would dictate adjuvant chemotherapy.

Future research should address these controversies and also long-term morbidity of systematic pelvic and para-aortic lymphadenectomy.

Concluding Comments

- There is a need to delineate the role of routine systematic lymphadenectomy in staging apparent early ovarian cancer. One option might be to randomize patients with high-grade serous and endometrioid cancers to this approach versus adjuvant chemotherapy, with node-negative patients receiving no further treatment. Quality of life should be included as an additional end point.
- Molecular markers may provide a better prognostic tool to identify those patients at high risk of recurrence in early-stage disease.
- Clear cell tumors need further appraisal in this context and should be considered separately to other subtypes.

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Part I

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Part II

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Sentinel Node Biopsy—Does It Help in the Management of Vulvar Cancer?

17

Maaike H.M. Oonk, Ate G.J. van der Zee, and Paul Speiser

Summary Points

The controversies that will be discussed in this chapter are:

- Safety of the sentinel node procedure/eligible patients
- Pitfalls of the sentinel node procedure
- Centralization of care for these patients/training considerations
- Quality of life

The Case for Sentinel Node Biopsy

Maaike H.M. Oonk and Ate G.J. van der Zee

The most recent improvement in the treatment of early stage vulvar cancer is the introduction of the sentinel lymph node procedure. Worldwide implementation of sentinel lymph node assessment in the treatment of early stage vulvar cancer followed after the GROningen INternational Study of Sentinel nodes in Vulvar cancer (GROINSS-V) proved its clinical value [1]. Although controversies remain regarding different aspects of sentinel node assessment, the procedure itself has been proven safe when performed in selected patients, by an experienced multidisciplinary team.

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Groin Recurrence Rate After Different Treatment Modalities

When discussing the safety of the sentinel lymph node procedure in vulvar cancer, the most important issue is the risk of increased frequency of groin recurrences. Groin recurrences are often fatal and therefore the most important threat for the patient. For a reliable comparison with respect to false-negative sentinel nodes and groin recurrence rates, one should compare the groin recurrence rates for patients after a negative sentinel node with patients who had no metastatic nodes at inguinal or inguinofemoral lymphadenectomy. Ideally a randomized trial should be performed in which patients with a negative sentinel node are randomized between observation and inguinofemoral lymph node dissection, comparable to similar studies in breast cancer [2]. Such a study has been designed (EORTC 55001) and proposed to large gynecologic oncology collaborative trial groups. However, this trial was deemed impossible due to the large number of patients needed ($n=680$) in relation to the low incidence of vulvar cancer. It is therefore unlikely that such a study will ever be performed, and thus decisions need to be made on level III and lower level evidence. One way to estimate the safety of the sentinel lymph node procedure is to compare the groin recurrence rate after sentinel lymph node biopsy to more invasive modalities for groin lymph nodes assessment, as reported in various cohort studies. Unfortunately only a few studies are available that report on groin recurrence rates after a negative lymphadenectomy. In addition these studies are difficult to analyze, because often different, not well-described surgical methods were used for the lymphadenectomy. Furthermore, the majority of studies are small and retrospective and only a few studies discuss the groin recurrence rates in node-negative patients separately.

However, it is obvious that the groin recurrence rate after more radical surgical techniques for groin treatment is very low (inguinofemoral lymphadenectomy en bloc or by separate incisions), varying from 0 to 4.7 % for lymph node-negative patients [3–8]. For superficial inguinal lymphadenectomy the groin

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recurrence rate seems to be higher: 0–8.7 % for lymph node-negative patients [9–14].

Groin recurrences are more often observed in patients with positive lymph nodes after inguinofemoral lymphadenectomy. In calculating the groin recurrence rate in these patients, numbers to compare are even smaller, as most patients will have negative lymph nodes. Also, differences exist in the application of adjuvant radiotherapy in these patients, not allowing proper comparison of results. From different retrospective studies, the groin recurrence rate after an inguino(femoral) lymphadenectomy with positive lymph nodes appears to be between 2 and 23 %, depending on the inclusion criteria of the study, the surgical technique, and the use of postoperative radiotherapy [1, 3–8, 14].

Since until recently inguinofemoral lymphadenectomy via separate incisions was the standard of care for patients with early stage vulvar cancer with a depth of invasion of >1 mm, groin recurrence rates in patients with a negative sentinel lymph node should be compared with this treatment approach. Based on reported data in literature as summarized above, the frequency of groin recurrences for this patient category can be estimated to be somewhere between 0 and 4.7 % for patients with negative nodes. As in this estimation retrospective studies are also included, it may well be that the real groin recurrence rate is higher, due to publication bias and underreporting of false-negative cases.

Results of Sentinel Lymph Node Procedure in Vulvar Cancer

After a few small pilot studies showed that the sentinel lymph node procedure in early stage vulvar cancer was a feasible technique, various accuracy studies were performed, in which the sentinel node procedure was followed by completion inguinofemoral lymphadenectomy. These studies showed that the sentinel lymph node procedure with the combined technique (use of blue dye and a radioactive tracer) had the highest identification rate and that the negative predictive value of a negative sentinel lymph node was very high [15]. However, two recent large studies showed unexpected high false-negative rates. First, the study performed by Hampl et al. reported an identification rate of nearly 100 % (125 out of 127 patients) and three false-negative sentinel lymph nodes (false-negative rate of 7.7 %) [16]. This false-negative rate was high compared with the results reported in literature until then. An explanation might be the inclusion of T1–T3 vulvar cancers on the basis that radical excision was possible. Multifocality was also not an exclusion criterion. All three tumors with a false-negative sentinel lymph node were located in the midline and two of these occurred in patients with tumors of at least 4 cm (40 and 56 mm), indicating that larger tumors might be less suitable for this approach. Experience with the sentinel lymph node procedure was not a requirement to participate in this multicenter study, which might be another explanation for the higher false-negative rate. In 2010, Radziszewski et al. also published their experience with the sentinel lymph node procedure [17]. They included 56 patients and found a false-negative sentinel node in seven cases. This extremely high number of false-negative cases is explained by the authors as due to lack of surgeons' experience. Indeed, the procedure was performed in 56 patients in a period of 5 years by a team of six surgeons/gynecologists, resulting in a mean of only two cases per surgeon per year.

At the end of 2012 Levenback et al. published the results of the largest multicenter trial on the diagnostic accuracy of the sentinel node procedure in vulvar cancer [18]. Patients with squamous cell cancer of the vulva with a tumor size of ≥2 cm and ≤6 cm were included. All women underwent intraoperative lymphatic mapping, sentinel node biopsy, and inguinofemoral lymphadenectomy. Histologic ultrastaging of the sentinel lymph node was performed. The sentinel lymph node was identified in 418/452 patients (identification rate of 92.5 %). A positive sentinel lymph node was found in 121 patients, and 11 had a false-negative sentinel lymph node. Despite the fact that again previous experience with the procedure was not required for participation, an overall negative predictive value of 96.3 % was observed, while for patients with a tumor <4 cm, the negative predictive value was 98 %. It was concluded by the authors, that the sentinel lymph node procedure appears to be a reasonable alternative to inguinofemoral lymphadenectomy in selected women with squamous cell cancer of the vulva.

Only a few studies have been reported in which inguinofemoral lymphadenectomy was not performed in the case of a negative sentinel lymph node. The largest of this type of validation studies is the GROINSS-V (GROningen INternational Study on Sentinel nodes in Vulvar cancer). This prospective observational study reported on 403 patients with early stage squamous cell vulvar cancer (T1/T2 tumors <4 cm and no suspicious groin nodes on palpation). The sentinel lymph node procedure was performed with the combined technique and a preoperative lymphoscintigram was made to identify the number and site of the sentinel lymph nodes. Multifocality became an exclusion criterion during the course of the study, because in a relative short period of time two groin recurrences occurred in patients with multifocal disease. A groin recurrence rate of 2.3 % in 259 patients with unifocal vulvar cancer and a negative sentinel lymph node was observed. GROINSS-V also demonstrated a major decrease in short- and long-term morbidity in these patients, who only underwent sentinel lymph node biopsy without subsequent inguinofemoral lymphadenectomy. Lymphedema was observed in only 1.9 % of patients after sentinel lymph node biopsy alone, compared to 25.2 % in patients who also underwent inguinofemoral lymphadenectomy. For recurrent erysipelas the percentages were 0.4 and 16.2 %, respectively. Based on an in-depth analysis of false-negative cases, which showed that significant failures in the procedure may occur due to mistakes by nuclear medicine staff, pathologists, and/or the gynecologic oncologists—the authors emphasize that the sentinel node procedure should

only be performed by a quality-controlled (for each member) multidisciplinary team [1].

Reade et al. performed a review to determine the clinical effectiveness, cost-effectiveness, and organizational feasibility of the sentinel node procedure in the Canadian health-care system. They found a groin recurrence rate after a negative sentinel node of 3.6 % compared with 4.3 % after a negative lymphadenectomy and reduced complications after sentinel node biopsy. They stressed that safe implementation of the sentinel node procedure requires appropriate patient selection, optimal detection techniques, and attention to the learning curve [19].

A recent retrospective study from the Surveillance, Epidemiology, and End Results (SEER) database on patients with vulvar cancer also indicated that the sentinel node procedure was not associated with an excess risk of mortality or recurrence [20].

Finally, some hypothetical calculations show that when 1,000 patients are treated for early stage vulvar cancer, approximately 200 patients will have inguinofemoral lymph node metastases. If we assume a groin recurrence rate of 3 % after a negative sentinel lymph node (a reasonably established figure) and 1 % after a negative inguinofemoral lymphadenectomy (very optimistic and not based on a large prospective series of patients), 24 patients will have a groin recurrence after a negative sentinel node (3 % of 800), while after an inguinofemoral lymphadenectomy eight patients will develop a groin recurrence. With this very optimistic estimation of the groin recurrence rate after inguinofemoral lymphadenectomy, these figures show that in order to prevent 1 groin recurrence 50 inguinofemoral lymphadenectomies need to be performed.

Sentinel Lymph Node Biopsy: Technical Pitfalls

A sentinel lymph node totally replaced by tumor may cause stasis of lymph flow and might be a cause of failure of sentinel lymph node detection [21, 22]. Therefore, enlarged nodes should always be removed, even when not found to be blue or hot at the sentinel node procedure. Preoperative imaging of the groins with ultrasound, CT, or MRI is recommended to exclude gross nodal involvement prior to the procedure. Patients who had previous radio(chemo)therapy of the vulvar/groin area should probably also be excluded for sentinel lymph node procedure since damage to the lymph vessels might cause failure of the procedure [23]. Based on the results of GROINSS-V, we also believe that multifocal tumors should be excluded.

Sentinel Lymph Node Biopsy: Training Considerations

The studies mentioned above by Hampl et al. and Radziszewski et al. stress the fact that the sentinel lymph node procedure should only be performed in centers in which high numbers of early stage vulvar cancer patients are treated [16, 17]. These centers should have an experienced team at every level of the multistep procedure (nuclear medicine department, gynecological department, pathology department). In GROINSS-V, a high quality of the sentinel node procedure in participating centers was ensured by determining that each gynecologic oncology center needed to have documented successful experience with the sentinel lymph node procedure with subsequent inguinofemoral lymphadenectomy in at least ten vulvar cancer patients. This is also recommended for all centers that want to incorporate the sentinel lymph node procedure in standard care for early stage vulvar cancer patients. We believe an exposure rate of at least five to ten patients per year is a minimum to keep experience at a high level. This requires centralization of these cases in oncology centers. Gynecologic oncologists who have very low incidence of vulvar cancer in their practice should consider referring vulvar cancer patients who are suitable for sentinel node procedure to a center with higher volume of patients. If for a variety of reasons patients do not want to be referred and local experience of sentinel node biopsy is nonexistent, inguinofemoral lymphadenectomy should be performed in order to avoid underdiagnosis with its possible serious consequences.

Sentinel Lymph Node Biopsy: Quality of Life

The sentinel node procedure has been introduced in vulvar cancer treatment to reduce morbidity and to improve quality of life. However, studies on this issue are limited. In vulvar cancer a quality of life study in 62 patients comparing patients who underwent sentinel node biopsy only to those with subsequent inguinofemoral lymphadenectomy did not support the original idea that a decrease in especially long-term morbidity also translates into an improved overall quality of life. This study was probably underpowered to detect small differences in global quality of life [24].

Recently, Novackova et al. studied the quality of life before and 6 months after vulvar surgery in 29 patients (17 inguinofemoral lymphadenectomy, 12 sentinel node biopsy). After vulvar surgery, patients who underwent inguinofemoral lymphadenectomy reported more fatigue and worsening of physical and role functioning. These patients had, compared with those who underwent sentinel node biopsy, significantly worse parameters in social functioning, fatigue, and dyspnea [25].

In breast cancer, more and larger studies are available on this subject. A recent prospective study in 829 breast cancer patients by Fleissig et al. showed that quality of life was better after sentinel node biopsy compared with axillary lymph node dissection [26]. Rietman et al. also showed in 181 breast cancer patients that 2 years after surgery, breast cancer patients who underwent sentinel node biopsy had significant less treatment-related morbidity and less worsening of quality of life compared to those who underwent axillary lymph node dissection [27].

To obtain more information on the impact on quality of life in vulvar cancer patients after sentinel node biopsy,

prospective quality of life studies should be performed in larger groups of patients at various times in their treatment and during follow-up. Data now available are insufficient on quality of life issues after sentinel node biopsy.

Summary

The sentinel node procedure in early stage vulvar cancer is a safe procedure when performed by an experienced multidisciplinary team in selected patients. Groin recurrence rates after a negative sentinel node are at least comparable to groin recurrences rates after more conservative surgical techniques with negative inguinofemoral lymph nodes. Patients eligible for this procedure should have T1a/1b tumors, smaller than 4 cm, without suspicious groin nodes at palpation. Since gross nodal involvement may cause false-negative sentinel nodes, we also recommend routine preoperative imaging by ultrasound, CT, or MRI, depending on local expertise. Concentration of care for vulvar cancer patients in high-volume gynecologic cancer centers is essential to keep the experience of all involved medical specialists at a high level. Only when these preconditions are met can the sentinel node procedure be incorporated in the standard care for early stage vulvar cancer patients. Under these conditions, the sentinel node procedure is a less morbid and safe alternative for inguinofemoral lymphadenectomy.

The Case Against Sentinel Node Biopsy

Paul Speiser

Only a little improvement in stage-related survival of women with gynecologic malignancies has eventuated over the last few decades. In contrast, the effort to decrease morbidity has been very successful. Vulvar cancer is a very good example not only to illustrate the success of this approach but also to demonstrate some limitations.

Reduction of Treatment Morbidity of Early Vulvar Cancer: Modifying Standard Surgical Procedures

The specific short- and long-term morbidity of vulvar cancer treatment such as wound breakdown, lymphocyst formation, lymphedema resulting in cellulitis and leg pain, and psychosexual problems is high and primarily related to the degree of radicality of the surgical approach in the resection of the primary tumor and the inguinofemoral lymph nodes [28–31].

Reducing the degree of radicality of resection of the primary tumor from radical vulvectomy, with en block inguinofemoral lymph node dissection (LND) to wide local excision with a 1 cm margin and inguinofemoral lymphadenectomy through separate incisions, has resulted in better sexual function and the preservation of structures vital for quality of life (QOL) such as the clitoris and distal part of the urethra, without compromising on the prognosis [32–39]. Local recurrences of the vulva are very amenable to local excision and carry an excellent prognosis.

Table 17.1 Groin recurrence rates with negative nodes after inguinal-femoral LND

	Number of patients	Recurrence (%)
Hacker et al. [40]	75	0 (0 %)
Burger et al. [41]	119	0 (0 %)
Bell et al. [42]	39	0 (0 %)
Rodolakis et al. [43]	211	3 (1.6 %)
Gonzales Bosquet et al. [44][a]	200	0 (0 %)
Tantipalakorn et al. [45]	102	0 (0 %)
	746	3 (0.4 %)

[a]17 patients with more superficial dissection excluded

Vulvar cancer is prone to metastasize into the groin lymph nodes even when only superficially invasive. Many authors have demonstrated that removal of the superficial inguinal and deep femoral lymph nodes in these patients results in significant morbidity but excellent local control with a groin recurrence rate of about 0.5 % (Table 17.1) [40–45]. Excellent groin control is particularly important because groin recurrence in vulvar cancer patients will in most cases be fatal [46, 47].

Less successful has been the attempt to cut back on the radicality of the inguinofemoral lymph node dissection in early stage vulvar cancer [29, 44, 48–52]. The GOG prospectively studied the effect of sparing patients from resection of the deep femoral nodes [29]. Although only very low-risk patients (depth of invasion ≤5 mm, no vascular space invasion, negative inguinal nodes) were entered in this study, a high rate of groin recurrences eventuated (6 of 121; 4.9 %). Gordinier et al. demonstrated that groin recurrences in patients spared from resection of deep femoral nodes frequently occur in non-resected lymph nodes (7 out of 9) [50]. Furthermore one study in node-negative vulvar cancer even found an improved survival with a greater number of lymph nodes removed, possibly as a result of removing microscopic disease [53]. Although it was clearly shown that with this approach the incidence and degree of leg edema was reduced, this was at the cost of a higher rate of groin recurrences (5.7 % vs. 0.5 %) (Table 17.2).

Reduction of Treatment Morbidity of Early Vulvar Cancer: The Sentinel Lymph Node Concept

The frustrating findings that a less aggressive surgical approach to groin lymph node resection in early stage vulvar cancer resulted into a higher rate of groin recurrences and compromised

Table 17.2 Groin recurrence rates with negative nodes after modified groin dissection

	Number of patients	Recurrence (%)
Berman et al. [48]	49	0 (0 %)
Stehman et al. [29]	121	7 (5.8 %)
Burke et al. [49]	76	4 (5.3 %)
Gordinier et al. [50]	104	9 (8.7 %)
Gonzales Bosquet et al. [44][a]	17	1 (5.8 %)
Kirby et al. [51]	65	3 (4.6 %)
Woolderink et al. [52]	91	6 (6.6 %)
	523	30 (5.7 %)

[a]200 patients with inguinofemoral dissection excluded

the patient's prognosis prompted a new approach trying to identify and biopsy the sentinel lymph node (SLNB) only. According to the SLN hypothesis, tumor cells migrate from a primary tumor and colonize one or a few SLN before involving other lymph nodes. The first area to receive lymphatic drainage from a lateral vulvar lesion is usually the ipsilateral superficial inguinal node region. At least in theory, if the SLN shows no evidence of metastatic involvement, then all other nodes should be negative, rendering complete nodal dissection unnecessary. The major concern with this approach is the false-negative lymph node rate, since leaving positive nodes behind will worsen the prognosis drastically [46, 47].

Sentinel Lymph Node Biopsy: False-Negative Sentinel Lymph Node

To date there is no prospectively randomized trial available to prove the concept of SLNB, largely because vulvar cancer is a rare disease, making such a study unfeasible. Experience with this approach is thus limited to observational studies.

The first large international observational study (GROINSS-V) used a combination of radioactive tracer and blue dye to detect sentinel nodes in 403 women with squamous cell vulvar cancer (tumor size <4 cm). After removal of the sentinel node it was then ultrastaged. No further treatment was given if an SLN was detected and was negative ($n=276$). If an SLN was positive or not detectable, inguinofemoral LND was performed. After a median follow-up of 35 months the groin recurrence rate in women with unifocal vulvar cancer and a negative SLNB was 2.3 %. The median time to groin recurrence was 12 months. Data were not reported for patients who had undergone LND. Long-term morbidity was significantly less common in patients receiving SLNB compared to inguinofemoral lymphadenectomy (lymph edema 1.9 % vs. 25.2 %, recurrent cellulitis 0.4 % vs. 16.2 %) [54].

Less favorable results were reported by a multicenter study from Germany involving seven centers in which 127 women with squamous cell vulvar cancer (T1–T3) were studied applying technetium-labeled nanocolloid and/or blue dye. After removal of the sentinel node, in all women a complete inguinofemoral lymphadenectomy was performed. The sentinel lymph node was detected in 98 % of cases with a lymph node positivity rate of 30.7 %. Three cases with a false-negative sentinel node were detected (false-negative rate 7.7 %). In one additional case the sentinel node was false-negative on the left side and positive on the right, increasing the false-negative rate to 10.3 % [55]. For informed consent this study needs to be explained to patients as follows. If 100 patients are treated using the SLN technique a lymph node metastasis will be missed in two to three cases putting you at high risk of dying from disease.

A single center study from Poland confirmed these less favorable results, even when combining both technetium-labeled nanocolloid and blue dye. Fifty-six patients with clinical early stage vulvar cancer (<4 cm) underwent the SLN detection procedure followed by a complete inguinofemoral lymphadenectomy. An SLN was detected in 99 % of all 109 groins dissected and submitted for histological examination by hematoxylin-eosin staining and cytokeratin immunohistochemistry. In 26 cases lymph node metastases were detected including seven that were negative on SLNB, resulting in a false-negative rate of 27 % [56]. For informed consent this study needs to be explained to patients as follows. If 100 patients are treated using the SLN technique in six to seven cases a lymph node metastasis will be missed, resulting in a significant risk of death.

The high rate of false-negative SLNB was confirmed in a recently published study by the GOG (GOG 173). Four hundred and fifty-two women with squamous cell cancers of the vulva with a tumor size between ≥2 cm and ≤6 cm underwent intraoperative lymphatic mapping and SLNB followed by inguinal femoral lymphadenectomy. In 132 patients the SLN was positive. False-negative SLNs were identified in 11 patients, resulting into a false-negative rate of 8.3 % [18]. If 100 patients are treated using the SLN technique in two to three cases a lymph node metastasis will be missed, putting you at a high risk of dying from the disease.

Sentinel Lymph Node Biopsy: Technical Pitfalls

In analyzing why the performance of sentinel lymph node biopsy varies to such an extent from center to center, one needs to take a number of aspects into consideration.

In the past blue dye alone, with a detection rate of 56–88 %, was used for sentinel lymph node identification making comparison of data difficult with the combined technique with technetium-99 m-labeled nanocolloid with a detection rate of 95–100 % [57]. Today most experts recommend combining the techniques. This means that an interdisciplinary approach is needed with dedicated specialists in nuclear medicine, making the system more complex and prone to error, error that might be fatal for the patient.

The learning curve for all specialists involved is another important issue, not only for gynecologist and staff of the nuclear medical department, but also the pathologist because there are several methods for intra- and postoperative evaluation. Issues like loss of lymph node tissue due to the technique of frozen section, step sectioning, ultrastaging with immunohistochemistry or molecular techniques, and finally the interpretation of the results are not standardized [58–60]. This is of particular concern, because the GROINSS-V study demonstrated that even when only isolated tumor cells were found in the SLN, the chances for additional metastases in non-sentinel lymph nodes were still about 4 % and these findings have been supported by others [54, 61].

Special clinical circumstances need special consideration. Over the past decades the proportion of HPV-dependent multifocal disease has steeply increased. During the course of the GROINSS-V study [54] these cases were excluded since it became evident during the study that they are not suitable for the sentinel approach. The same is true for obese patients whereby passing of the sentinel node is of concern [62]. This further reduces the small number of cases available for training purposes or to maintain the level of expertise needed for safe practice.

Furthermore sentinel lymph nodes completely replaced by tumor frequently lead to stasis of the lymphatic flow resulting either to flow to another lymph node that will stain and be misinterpreted as a sentinel lymph node or to nonvisualization of the sentinel node. This situation requires significant clinical experience because the positive node will only be identified through careful intraoperative palpation of the entire groin region, partly requiring no resection but sometimes significant dissection of the tissue. Because of these circumstances many experts strongly recommend MRI or CT of the groins preoperatively [63].

Sentinel Lymph Node Biopsy: Training Considerations

Vulvar cancer is a rare disease [64] and the degree of centralization in most countries is poor, leaving each gynecologist operating only on a very small number of vulvar cancer patients each year. This usually is not a problem for an experienced surgeon, as long as routine standard surgical techniques are involved. A major issue in the use of SLNB is the learning curve depending on the surgeon's skills and experience. For vulvar cancer the number of cases required to render a surgeon capable of performing a sentinel lymph node procedure is still undefined. In breast cancer SLNB is well established and still the yet recommendations vary in regard to the minimal number of cases need to train a breast surgeon to become competent in the procedure. Between 20 and 60 cases are suggested as a minimal number of SLNB procedures, either supervised by a surgeon experienced with the procedure or followed by axillary lymph node dissection to minimize the risk of false-negative results [65–67]. For breast cancer, a cancer that is approximately 50 times more common as than vulvar cancer, studies have shown that the time frame of the learning curve is of concern. Courses are now offered in SLNB technique in breast cancer and are considered a prerequisite of training. The technique is most rapidly learned by one-on-one training with an experienced surgeon [68]. The excellent nodal recurrence rate after SLNB in breast cancer (0.1–0.3 %) cannot be extrapolated to vulvar cancer, since most breast cancer patients will receive some sort of adjuvant treatment, even in node-negative disease.

Vulvar cancer is a rare disease affecting fewer than 4,000 patients in the United States each year [64]. The GOG trial entered 452 women over a period of approximately 9 years from 47 member institutions. This calculates to not even ten patients in 9 years per center. In the GROINSS-V study the University Medical Center of Groningen, a high-volume center for vulvar carcinoma, entered 115 patients in 6 years [54]. In this center only two gynecologic oncologists performed SLNB, leaving each with less than ten cases per year.

In the single center study from Poland all patients were operated by a team of six surgeons. Discussing their results, the authors concluded that it is highly probable that the main factor responsible for the high false-negative SLN number in their study was the surgeons' experience. Although all of the operations were performed by surgeons and gynecologists with at least 15-year experience, the SLN detection procedure, according to the protocol used, was performed only a few times by each [56].

In its expert panel statement in 2008 the International Sentinel Node Society recommended that an individual gynecologic oncologist perform at least ten consecutive cases with successful SLN identification and no false-negative results before performing SLNB without lymphadenectomy [69]. For most centers in the United States of America and the European Union these requirements will be hard to meet, particularly within a time frame that would be acceptable.

Sentinel Lymph Node Biopsy: Quality of Life

The concept of SLNB was developed to reduce long-term morbidity in vulvar cancer treatment and to increase quality of live (QOL). The hypothesis that reduction of long-term morbidity by SLNB will result in a better QOL was examined in two studies. Structured questionnaires were sent to both patients and gynecologists [24, 70]. In one study, the response rate among 117 patients in complete remission after inguinofemoral lymph node dissection for a positive SLNB at the Groningen University Hospital between 1985 and 1993 was 91 %. Approximately 40 % reported on one or more infections in the leg (cellulitis) and 49 % on either severe lymphedema or

severe pain in the leg. Patients were asked whether they would have preferred the less morbid procedure of SLNB with a hypothetical risk that in 100 patients with early stage vulvar cancer one patient with a positive lymph node would have been missed. For 66 % of patients this risk was not acceptable and they preferred the significant morbidity of the more accurate surgical procedure over the risk of missing a positive node. The response rate of gynecologists was that 80 and 60 % of them were willing to accept a false-negative SLN result in 1–4 out of 100 early stage vulvar cancer cases. This clearly demonstrates that patients are far less willing to take a potential risk that frequently is fatal [70].

A more recent report also used structured questionnaires to assess differences in the QOL of patients who participated in the GROINSS-V study who underwent inguinofemoral lymphadenectomy for a positive SLN ($n=27$) [24]. They were compared to age-matched patients who received an SLNB only ($n=35$). Furthermore what these patients would advise their relatives on the use of SLNB in light of its supposed false-negative rates was evaluated. As expected a vulvar specific questionnaire revealed significantly more long-term morbidity (leg edema and discomfort in groins, vulva, and legs) in the lymphadenectomy group. Differences in QOL were studied using the validated EORTC QOQ-C30 questionnaire. There was absolutely no difference in Global Health Status and QOL. This phenomenon was also studied in other cancers. Surviving cancer obviously coincides with attitudinal changes and changes in internal standards, values, and the conceptualization of health-related QOL [71, 72].

The information, that SLNB will most likely not impact on the Global Health Status and QOL compared to LND, is very important for counseling patients diagnosed with early stage vulvar cancer. Informed consent implies that the patient has all information available to carefully balance the potential benefits against potential risks.

Summary

Standard inguinofemoral lymph node dissection (LND) for early stage vulvar cancer results into excellent groin control (0.5 % groin recurrence rate) but with significant long-term morbidity like leg edema, cellulitis, and leg pain in 50 % of patients. Sentinel lymph node biopsy (SLNB) reduces the risk of long-term morbidity to <10 %. To date, it is not possible to demonstrate that this reduction impacts on quality of life (QOL). Out of 100 patients the SLNB will miss lymph node metastases in two to four patients, resulting in an increase of fatal groin recurrences by four to eight times compared to LND. Sixty-six percent of patients preferred a 50 % risk of long-term complication over a 1 % risk of missing one positive node during SLNB. Sixty percent of gynecologists were willing to accept false-negative SLN result in 1–4 %. Even in large centers, single gynecologists treat far less than ten patients with early stage vulvar cancer per year. Contraindications to SLNB like obesity, HPV-dependent multifocal disease further reduce the number of patients potentially eligible for SLNB. Issues like adequate training, standardization of histopathological work-up, and false-negative results are not resolved and most likely will not be resolved in the near future. SLNB compromises survival and is therefore not acceptable to the majority of patients.

Concluding Comments

- The sentinel node procedure is safe when performed in selected patients by an experienced multidisciplinary team.
- Concentration of care for vulvar cancer patients in high-volume gynecologic cancer centers is essential to keep the experience of all involved medical specialists at a high level.
- Since no randomized controlled trials are available, it remains difficult to compare survival between patients who underwent standard inguinofemoral lymphadenectomy to those in whom the sentinel node procedure was performed.
- There is no evidence to date that the reduction in treatment-related morbidity that coincides with the sentinel node procedure also reflects in an increase in quality of life (QOL).

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Controversies in the Management of Advanced Vulvar Cancer

18

Ericka Wiebe, Jacobus van der Velden, and Gillian Thomas

Summary Points

- Adequate oncologic surgery to either the site of the primary lesion or the involved lymph nodes in advanced vulvar cancer may be difficult to achieve without potential surgical morbidity; therefore, multimodality therapy that integrates radiation with or without chemotherapy to lessen the extent of surgery has become commonplace. However, the optimal delivery of multimodality therapy for advanced vulvar cancers is not clearly defined, and the controversies in determining when and how to combine therapies are explored.
- Definitive chemoradio therapy and neo-adjuvant chemotherapy for advanced vulvar lesions are controversial due to limited supporting evidence; expert opinion is provided.
- Individualized treatment remains critically important in the management of recurrent disease and palliation.

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Introduction

There are many controversies surrounding staging and management of advanced vulvar cancer. TNM and FIGO staging (Table 18.1) [1] result in heterogeneity within groupings with respect to prognosis. For example, a stage T3 tumor may be 2 cm in size involving the vagina only and can be treated without major reconstruction or stoma formation. However, if a T3 tumor invades the rectal mucosa, radical resection would necessitate a colostomy. There is no universally accepted definition of advanced cancer; for this chapter, "advanced disease" will include tumors where primary surgery alone is insufficient for optimizing the probability of control and maintaining functional integrity. This will include patients with variable prognoses.

Although vulvar cancer is rare, with an annual incidence of 2–3 per 100,000 women, it is estimated that T3/T4 disease occurs in approximately 20 % of patients at clinical presentation, and approximately 30 % will have identified inguinofemoral lymph node involvement [2, 3]. This relative rarity of vulvar cancers limits Level 1 evidence to guide management.

Historically, advanced vulvar cancer was treated with radical vulvectomy with bilateral inguinal lymph node dissection, with or without pelvic lymph node dissection, and often including exenterative surgery with stoma formation. Overall survival ranged from 25 to 40 % in "locally advanced disease," with high rates (24–85 %) of acute wound breakdown, and 30–70 % rates of leg edema [4]. To avoid stoma formation, pioneers such as Boronow et al. [5] and Hacker [6] developed treatment approaches incorporating radiotherapy and permitting less radical surgery. Integration of radiotherapy (RT), and subsequently chemoradiotherapy (CRT), has improved the therapeutic ratio. Such approaches have resulted not only in avoidance of exenterative surgery but also in improved 5-year disease-specific survival rates of 50–60 % [3]. In a population-based evaluation, rates of treatment of advanced disease with surgery alone have declined from 40 to 25 % over the past two decades [3].

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Table 18.1 FIGO staging for carcinoma of the vulva

Stage	Description
I	Tumor confined to the vulva
IA	Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm[a], no nodal metastasis
1B	Lesions >2 cm in size or with stromal invasion >1.0 mm[a], confined to the vulva or perineum, with negative nodes
II	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
III	Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes
IIIA	
(i)	With one lymph node metastasis (≤5 mm)
(ii)	One to two lymph node metastasis(es) (>5 mm)
IIIB	
(i)	With two or more lymph node metastases (≤5 mm)
(ii)	Three or more lymph node metastases (>5 mm)
IIIC	With positive nodes with extracapsular spread
IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina) or distant structures
IVA	Tumor invades any of the following:
(i)	Upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone
(ii)	Fixed or ulcerated inguino-femoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

Adapted from Pecorelli [1]
[a]The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion

Incorporation of multimodality therapy results in additional complexity in decisions regarding patient management and points to a role for specialized multidisciplinary expertise. The challenge in management decisions is to define treatment tailored to disease extent, integrating the advantages of each modality. Patient-related factors increase controversy around choosing optimal therapy, since patients are often elderly and have significant medical comorbidities [3, 7, 8]. The extent of disease and comorbid factors needs to be considered for each individual patient. Decision-making surrounding multimodality management is complex; therefore, optimal management should be based on specialized expertise.

Treatment of Primary Vulval Cancer

Controversy: When to Proceed with Surgery?

Surgery needs to be considered when a vulvar lesion can be resected without functional compromise to midline structures and with an adequate surrounding margin. In the rare situation where there is involvement of the distal urethra that remains limited (less than the distal third), surgery with excision of not more than 1.5 cm of the distal urethra may provide a therapeutic option that does not compromise urinary continence [9]. Of the 10 % of patients with anal involvement, there may be a very small minority in which limited resection of the anal mucosa or skin may preserve the anal sphincter [10]; partial or total resection of the external anal sphincter is required in more extensive tumors. While total excision of the anal sphincter is expected to result in fecal incontinence, whether a part of the sphincter can be removed without compromising the fecal continence is difficult to establish due to the paucity of prospective or controlled data [10].

In the clinical decision-making regarding resection of a vulvar cancer approaching midline structures, the tumor-free margin must also be taken into account. Retrospective surgical data found that margins of less than 8 mm had a local recurrence rate of 48 % [11]. The importance of margin status in achieving local control is supported by multivariate analysis in addition to some retrospective surgical series [12–14], but recently refuted by others [15]. In the latter series, unfortunately, the issues of surgical re-excision and the use of adjuvant radiotherapy confound the conclusions that can be drawn regarding the importance of adequate margins. A general recommendation for a planned surgical margin of 1 cm will take into account 20 % shrinkage as a result of formalin fixation [16]. However, in a study by de Hullu and co-workers, an intended surgical margin of 1 cm resulted in a pathological margin of <8 mm in 50 % of patients [17]. Therefore a surgical margin of 2 cm was recommended, but the impact of a wider surgical margin on lowering local recurrence rates is unclear [14]. In light of the importance of a pathological margin of at least 8 mm, surgical clearance of 1 cm is recommended as a minimum requirement.

Table 18.2 Collated literature data on survival after exenterative surgery in advanced or recurrent vulvar cancer

Authors	*n*	P/Rec Disease (n)	% RT	Anterior/posterior/complete Exenteration (n)	DFS (Pr/Rec) (%)	OS (Pr/Rec) (%)	Mortality (%)
Forner and Lampe [19]	27	9/18	100 %	17/4/6	67/59 %	56/61	0 %
Miller et al. [20]	21	8/13	69 %	6/12/3	50 %/31 %	70/38	0 %
Hoffman et al. [21]	24	21/3	na	4/17/3	na	46	4 % ($n=1$)
Hopkins and Morley [22]	19	11/8	25 %	na	na	61/38	0 %

DFS disease-free survival, *OS* overall survival, *Pr* primary disease presentation, *Rec* recurrent disease presentation, *RT* radiation therapy

Controversy: Is There a Role for Primary Pelvic Exenteration (When Tumor Features Compromise Ability to Achieve Clear Margins with a Wide Local Excision or Modified Radical Vulvectomy)?

Lesions that are in close proximity or involving vertical midline structures (clitoris, urethra, anal sphincter) cannot be resected without either compromise to the width of the margin achieved or surgical morbidity from exenterative or partially exenterative procedures. Despite this, there is no widely accepted definition of "operable" versus "inoperable" vulvar cancers. Scenarios of tumors fixed to pelvic structures or of extremely large size (necessitating major reconstructive surgery) may not be appropriate for surgical management. There are no randomized trials of chemoradiation versus surgical management of locally advanced disease. Retrospective case series are often imbalanced with respect to patient- and tumor-related factors that influence physician choice of one treatment over another [18]. Exenterative surgery may be particularly difficult for elderly patients who have greater difficulty managing multiple stomas. Conversely, patients experiencing painful symptoms from the primary tumor may have difficulty tolerating a radical chemoradiation therapy (CRT) approach and should have consideration for prompt symptom control with a surgical approach.

Studies reviewing the results of pelvic exenteration (PE) in patients with advanced vulvar cancer frequently include patients with recurrent vulvar cancer, many of them pretreated with radiotherapy. In published series, 5-year survival rates of patients treated with exenteration in the primary setting are approximately 60–70 %, while survival after surgical management of recurrent disease is much lower at 40–60 % (Table 18.2) [19, 20, 22]. Clear margins at PE and the absence of lymph node involvement are important prognostic factors for survival after PE [19, 21, 22]. The status of the inguinal lymph nodes significantly influences the outcomes achieved, with 5-year survival rates of 70–80 % in patients with negative nodes, compared to 0–30 % when the inguinal lymph nodes are involved [19, 22]. Before performing an exenterative procedure in advanced or recurrent vulvar cancer, extra-pelvic metastases must be ruled out by imaging. Although computed tomography (CT) is routinely used for this purpose, the sensitivity of (18)-FDG positron emission tomography (PET)/CT is much higher for cervical and vaginal cancers and is therefore recommended [23].

Both primary exenterative surgery and primary radiation therapy (RT)/CRT may require additional modalities of therapy, with increasing complication rates in situations where additional therapies are required. CRT followed by less radical surgery may effectively avoid stoma formation. Primary PE should be considered in the rare presentation of rectovaginal or vesicovaginal fistulae. The decision regarding a role for exenterative surgery *versus* CRT should be made jointly between the surgeon and the radiation oncologist.

Controversy: What Is Optimal Postoperative Management for Risk Factors Predictive of Local Failure?

Management options for patients with risk factors for local recurrence (close or positive margins, lymphovascular-space invasion, tumor invasion greater than 5 mm depth [11]) include clinical surveillance, repeat surgical resection, or adjuvant RT/CRT. There is controversy regarding the success of salvage surgery *versus* the efficacy of adjuvant therapy, with no high-level evidence to guide the choice of one *versus* the other. Retrospective series provide some guidance regarding the potential efficacy of salvage therapy. Re-resection for recurrence resulted in local control in 56 % of patients [12], and survival after surgical management of local recurrence is reported at 51 % at 5 years [24]. If there is further vulvar cancer at a non-adjacent site, this is likely a new primary cancer for which surgical outcomes are more favorable. True recurrences tend to occur after a short disease-free interval, and survival is reported as only 15 % after 3 years [14]. Disease at distant vulvar sites, in contrast, occurs after a longer disease-free interval and 3-year survival rates are higher at 67 % [14].

If an involved margin is at the lateral aspect, repeat resection may offer a definitive management option, recognizing that additional pathologic risk factors for recurrence may remain. If the risk factor for recurrence is a close or involved deep margin, further resection may not be possible. Clinical surveillance may not be effective in identifying early recurrence, particularly at deep tissue planes, thereby leading to

decreased salvage rates. There is evidence that adjuvant RT/CRT may increase rates of local control. In a single-center retrospective series, local-regional recurrence was reduced with the addition of adjuvant radiation from 69 to 33 % in patients with positive margins ($n=28$) and from 31 to 5 % in patients with close margins ($n=34$) [25]. Although there was a benefit in reducing local recurrences with adjuvant radiotherapy in both groups, only the subgroup with positive margins showed a survival benefit after adjuvant radiotherapy [25]. Adjuvant radiation for close or involved margins is widely practiced, but it is unclear if it can overcome other pathologic risk factors for recurrence such as deep invasion (defined as >5 mm) and lymphovascular-space invasion. It is impossible to assess the relative benefits of observation and possible surgical salvage *versus* adjuvant treatment (re-resection or radiotherapy) with the limited data available.

Controversy: How to Optimize Adjuvant Radiation Therapy?

Vulvar squamous cell carcinomas are exquisitely sensitive to radiation therapy, as observed with complete resolution of 30 % of advanced T3/T4 lesions with modest radiation doses of 47.6 Gy given with concurrent chemotherapy [26]. Controversy surrounds the radiation dose required to optimize local control postsurgery where hypoxia may increase radiation resistance. Adjuvant radiation doses of 45–50 Gy are typically used for close margins, while higher doses, e.g., 50–54 Gy, are often used for positive margins [25]. For treatment of potential microscopic residuum, radiation without concurrent chemotherapy may be sufficient. Just as surgery has become limited to the site of vulvar disease rather than complete vulvectomy, radiation can be tailored to the surgical bed with appropriate margins. Often a perineal port with energy chosen according to the depth of the area at risk can be used, thus sparing unaffected regions of the vulva and minimizing the volume of radiation-associated acute and late skin toxicities.

Controversy: What Is the Role for Initial Versus Definitive Chemoradiaotherapy?

Where the primary is proximal to midline structures or is too extensive for functional preservation, initial CRT may be used. Incremental benefits of chemotherapy added to RT have been shown in other epithelial tumor sites including cervical, head and neck, and anal cancer [27–31]. In the latter, the anal sphincter preservation achieved with CRT is most analogous to the approach in vulvar cancer. By extrapolation, similar regimens have been used in the neo-adjuvant or primary treatment of vulvar cancer. Multiple retrospective studies of preoperative CRT for vulvar cancer have reported favorable rates of clinical response, local control and survival utilizing 5-FU and mitomycin C, or 5-FU and cisplatin [26, 32, 33]. Prospective studies of preoperative CRT have yielded high rates of clinical complete response (46 % for inoperable primary) [26] and high rates of preservation of urinary function and gastrointestinal continence. Of 40 patients with residual disease after CRT, only 2 patients had unresectable disease, and 5 patients had positive resection margins [26]. In 3 patients, urinary and/or GI continence could not be preserved with surgery [26]. However, these findings demonstrate that tumor may not reliably regress away from critical structures for complete surgical resection without exenteration or positive margins after CRT in all cases.

The success of CRT in the preoperative treatment of locally advanced vulvar cancers has lead to definitive management with chemotherapy and radiation without planned surgery. There is controversy whether superior outcomes can be achieved using higher doses of definitive CRT and resection only if potential residual disease, compared to preoperative CRT to shrink the tumor and planned resection of the residual tumor bed. An optimal radiation dose and fractionation scheme for definitive management has not been defined. An accumulation of data points suggests that there is a radiation dose response of vulvar cancer to CRT, with clinical complete response rates of 46 % with 47.6 Gy [26], compared to improved clinical complete response rates of 64 % using increased radiation doses of 57.6 Gy [34]. The modest doses of radiation used in these GOG studies (47.6–57.6 Gy) resulted in pathologic complete response rates (31–50 %) that did not uniformly correlate with the clinical response rates [26, 34]. Therefore, either consideration for completing radiation to a higher definitive dose of radiation, e.g., 62–64 Gy, or a surgical resection should be considered. In cases where there is obvious residuum, or an expectation of microscopic residual exists, methods for determining the necessary extent of surgery are ill defined. A mapping procedure, consisting of taking multiple biopsies of the tumor bed, could help in determining this extent. The aim of resection following RT/CRT is to remove all residual disease; rarely, this may require stoma formation.

Despite widespread use of CRT, optimal agents for concurrent chemotherapy with RT have not been defined [35]. Available prospective and retrospective studies do not allow assessment of the relative efficacy of varying chemotherapy regimens. Combination chemotherapy has been utilized; in GOG-101 chemotherapy consisted of 5-FU with cisplatin [26]. Similar to activity in the treatment of anal carcinoma [27, 36], mitomycin C and 5-FU may represent agents with high activity in vulvar carcinoma. However, a recent trial of CRT in anal carcinoma suggests that, although CRT with cisplatin and 5-FU CRT offers no local control advantage over mitomycin C and 5-FU, cisplatin-based chemotherapy may represent a viable alternative because of a more favorable toxicity profile [31]. Weekly

cisplatin has become the most commonly used regimen in CRT for vulvar carcinoma [35]; in GOG-205 chemotherapy consisted of single-agent cisplatin [34].

Controversy: Should Conformal Radiation Techniques Be Used?

Modern conformal radiation techniques such as intensity-modulated radiotherapy (IMRT) or tomotherapy may offer an opportunity to better deliver dose to tumor target volumes, while sparing radiation to close-by normal tissues. Since there is no consensus on how to implement such highly conformal radiation, its current use is controversial. An international survey of radiation oncologists revealed variation in the definition of target volumes for both primary and nodal regions [37]. Small series of patients treated with IMRT have been published [38]; however, comparative efficacy data and long-term results on tumor control and toxicity are lacking. Until consensus guidelines and quality assurance procedures are developed, highly conformal techniques remain investigational.

Controversy: Should Definitive Chemoradiation Therapy Be Avoided Because of Associated Morbidity?

The reported morbidity of CRT is acceptable, even in elderly populations [39]. While the morbidity is "acceptable," there remains the potential for severe toxicity and, rarely, treatment-related deaths [26, 40]. Comorbidities such as diabetes and smoking may increase treatment toxicity. The potential toxicity of CRT may be further reduced by a low daily radiation dose per fraction (≤175 cGy/day) and allowance for a treatment break when moist desquamation occurs. Although moist desquamation occurs in 100 % of patients undergoing definitive CRT, a short treatment break will allow sufficient re-epithelialization to complete a course of CRT. Because of the exquisite radiosensitivity of vulvar cancer, prolongation of the overall treatment time may not have the same negative impact in achieving local control as observed in cervical carcinoma [41, 42].

Controversy: Is There a Role for Preoperative Chemotherapy Alone?

If a decision has been made to treat a patient with surgery, but preoperative tumor reduction is sought, RT may contribute to problems with wound healing. Therefore the efficacy of preoperative chemotherapy without RT is being explored. Collated literature data (of studies including more than five patients) show objective responses in advanced and recurrent vulvar cancer between 10 and 100 % (Table 18.3). Although reported operability rates after chemotherapy have varied from 29 to 90 %, the definitions of operable were not well defined, and the patient populations were heterogeneous, precluding any meaningful comparison with operability after CRT. In addition, morbidity was high with up to 40 % of patients experiencing Grade 3 or 4 side effects, and even 8 % toxic deaths in one study [49]. Were more effective and less toxic chemotherapy to be identified in the future, one might be able to avoid RT in achieving preoperative tumor reduction and avoidance of stoma formation; unfortunately, at present these agents do not exist. Given the high response rates of vulvar carcinoma to CRT, it is unlikely that chemotherapy alone, with the currently available agents, can replace CRT.

Treatment of Lymph Nodes

Once vulvar cancers have a depth of invasion greater than 1 mm, the risk of lymph node involvement increases to 10–30 % [50], with very poor survival in the case of metachronous groin node recurrence [51, 52]. In a large population of patients with advanced vulvar cancer, two-thirds had a pathologic assessment of lymph nodes, and of these, only 13 % had negative nodes [3]; therefore, there is an obligation to manage the groin lymph nodes as part of initial management. For patients in whom the pelvic lymph nodes are also involved, only approximately 20 % achieve long-term disease-free survival [53]. Although the prognostic importance of groin and pelvic node involvement is well established, the optimal diagnostic and management approaches to the nodal regions in advanced vulvar carcinoma remain controversial.

Given the survival implications of untreated groin node involvement, management of the groin nodes is clearly indicated for any patients with tumor invasion greater than 1 mm depth. Additional pathologic risk factors that are predictive of lymph node metastasis include capillary space invasion, location of tumor, and tumor size [50, 54, 55]. However, depth is the most reliable indicator of lymph node involvement and is thus routinely utilized in determining appropriate management of the groin lymph nodes. Management of the groin lymph nodes can vary depending on the management of the primary site of disease.

Controversy: After a Positive Sentinel Lymph Node Biopsy, Does Primary RT/CRT to the Groins Constitute Safe and Effective Management?

Where the tumor size is limited to 4 cm or less and is unifocal, sentinel lymph node biopsy (SLNB) may be used to assess groin node involvement [13, 56]. SLNB has a high

Table 18.3 Collated literature data of neo-adjuvant chemotherapy (NACT) studies that included more than five patients

Reference	Evaluable patients (*n*)	Chemotherapy (*n*)	Toxicity	Response rate
Tropé et al. [43]	21	(a) Single-agent bleomycin (11)	"No severe side effects"	(a) CR, 2/11; PR, 3/11
		(b) Bleomycin and mitomycin-C (9)		(b) CR, 1/9; PR, 4/9
Durrant et al. [44]	28	Bleomycin, methotrexate, CCNU	Grade 3/4 toxicity: 10/25 2(8 %) toxic deaths (1 pulmonary fibrosis; 1 myelosuppression)	64 % (CR, 11 %) 29 % "operable" (8/28); 7 had surgery
Benedetti-Panici et al. [45]	21	Cisplatin, bleomycin, and methotrexate	Leukopenia Grade 1/2: 29.5 % Renal: 29 % (mild) N&V: 81 % (only severe in one patient) No pulmonary toxicity	Primary tumor: CR: 0/21 PR: 2/21 Nodes: CR: 11/21 PR: 3/21 79 % radical surgery after NACT (68 % recurrence after surgery)
Wagenaar et al. [46]	25	Bleomycin, methotrexate, CCNU	Two toxic deaths (8 %)	CR 2/25 (8 %) PR 12/25 (48 %) 10 "operable" (40 %); 8 had surgery
Geisler et al. [47]	13	(a) Cisplatin, and 5-FU (10)	Grade 3/4 GI: 2 (diarrhea, stomatitis)	(a) CR: 1/10 PR: 9/10 90 % underwent radical surgery
		(b) Cisplatin alone (3)		(b) 0 % response rate to cisplatin alone
Domingues et al. [48]	25	(a) Bleomycin (10)	The only registered Grade 3 or 4 toxicities were GI (incidence not given)	(a) 60 % response rate 1 CR, 5 PR; 6 radical surgery
		(b) Paclitaxel (5) (c) 5-FU/cisplatin (10)	No pulmonary fibrosis in the bleomycin group	(b) 40 % response rate 2 PR; 2 radical surgery (c) 20 % response rate 2 PR; 2 radical surgery

5-FU 5-fluorouracil, *CCNU* 1-(2-chloroethyl)-cyclohexyl-nitrosourea (lomustine), *CR* complete response, *GI* gastrointestinal, *PR* partial response, *N&V* nausea and vomiting

negative predictive value for groin lymph node metastases, with only a 2 % rate of groin recurrence after negative biopsy [13]. The benefit of a SLNB *versus* an inguinal-femoral lymphadenectomy (IFL) is a significant reduction in acute and chronic surgical complications including wound breakdown (11.7 *versus* 34 %), cellulitis (4.5 *versus* 21.3 %), and lymphedema (1.9 *versus* 25.2 %) [13].

A positive sentinel lymph node is associated with a 20 % risk of residual nodal disease [57]; however, optimal further management remains controversial. An international multicenter observational study of inguinal RT/CRT after positive SLN (GROINSS-V II) is ongoing to evaluate better the efficacy of nonsurgical management of the groins [58]. It is unclear whether nodal disease has the same radiosensitivity as the vulvar primary. GROINSS-V II was temporarily suspended for protocol amendment after high groin failure rates were observed. In 45 patients with a positive sentinel node on the basis of isolated tumor cells or micrometastases (diameter = <2 mm), only one groin recurrence was observed after radiotherapy, while in 36 patients with macrometastases (diameter >2 mm), nine (20 %) groin recurrences were observed [58]. The GROINSS-V II study has reopened and currently excludes patients with sentinel node metastases measuring greater than 2 mm. In these patients a complete IFL dissection followed by adjuvant radiation to a dose of 56 Gy is recommended.

Controversy: What Constitutes Optimal Surgical Management of the Groin Nodes?

Optimal surgical management of the groin lymph nodes consists of bilateral IFL through separate incisions, for patients with tumors on or in close proximity (1 cm or less) to the midline. It is important that both the superficial inguinal and the deeper femoral lymph nodes are removed. In patients where only the superficial nodes were removed and found to be negative, a 16 % groin recurrence rate was reported [59]. This is in contrast to series where a formal IFL was performed with groin recurrence rates less than 1 % [60]. Although IFL through separate incisions results in significantly lower morbidity compared

with the en bloc resection, there is still a high morbidity rate with 17 % wound breakdown, 39 % infectious problems, and 40 % lymphocyst formation [61]. Although some novel modifications to surgical technique, such as sartorius transposition and inguinal skin access above the ligament, have not demonstrated significantly decreased morbidity over standard IFL [62, 63], in an effort to lower surgical morbidity, sparing of the saphenous vein has been widely adopted, despite uncontrolled studies with low numbers of patients [64, 65].

Controversy: How to Manage the Groin When the Primary Vulvar Lesion Will Be Treated with CRT?

If CRT has been chosen to manage disease in the vulva, management of the groins is controversial and is influenced by the presence or absence of clinically apparent nodal disease.

Controversy: How Should Patients with No Clinically Involved Lymph Nodes Be Managed?

The dose of radiation necessary to sterilize involved nodes in an undissected groin is unknown. A small study of primary radiotherapy to the groin for clinical N0/N1 groin disease found inferior survival compared to surgery with or without adjuvant RT [66]; unfortunately, the RT dose received by groin nodes at a depth was inadequate [67]. Retrospective case-controlled data supports the use of irradiation of N0/N1 inguinal nodes as an alternative to surgery to reduce morbidity compared to IFL [68]; however, the efficacy of primary CRT to the groin is indeterminate since the number of patients with pathologically involved nodes has not been assessed. Primary CRT without knowledge of groin status can result in those with negative nodes being treated unnecessarily [54].

In advanced vulvar cancer where the primary tumor will be treated with CRT, patients who are node negative after IFL can proceed to vulvar CRT while the surgical healing of the groin is ongoing. But when nodes are pathologically involved, delayed groin healing may delay concurrent CRT of the vulva and groins. However, due to the uncertainty of groin control with CRT, IFL with appropriate adjuvant RT continues to be the standard of care for groin management.

Controversy: How Should Patients with Clinically Palpable Lymph Nodes Be Managed?

Given the uncertainty of groin control with CRT and that palpable fine-needle aspirate (FNA)-confirmed groin nodes represent more than microscopic disease, debulking may be an option for groin management. In a small retrospective series, nodal debulking, when compared with IFL, did not jeopardize survival outcome when surgery was followed by groin and pelvic radiation [69]. Groin node debulking followed by vulvar and groin CRT has the advantages of reducing the morbidity and potential treatment delay related to a complete IFL dissection, while providing control of local-regional disease. Alternatively, groin surgery to resect any residual clinically palpable or radiologically identified residual disease can be undertaken at completion of CRT.

Controversy: How Should Patients with Fixed/Ulcerating Lymph Nodes Be Managed?

For patients with fixed or ulcerating groin nodes, and in patients with clinical signs of dermal lymphatic involvement (*lymphangitis cutis*), initial groin node dissection is contraindicated. Furthermore, a high risk of dermal lymphatic invasion should be addressed using a radiation treatment plan with adequate coverage of areas of possible dermal lymphatic involvement. Lymphatic dye studies demonstrate dermal lymphatic drainage of the vulva coursing superiorly to the mons pubis, then laterally to the ipsilateral groin [70]. As demonstrated in GOG-101, preoperative CRT is highly effective in both reducing nodal tumor burden to allow resection and in obtaining control of regional disease [71]. CRT for unresectable lymph nodes has been shown to achieve pathologic complete response rates in 40 % of patients [71]. Eighty three percent of patients (38/46 patients) with initially unresectable lymph nodes were able to undergo surgery after preoperative CRT, and ultimately nodal disease was controlled in 36/37 (97 %) patients [71]. In order to achieve similar rates of long-term control, surgical removal of any residual clinically palpable or radiologically identified residual nodal disease should be undertaken after CRT.

Adjuvant Radiotherapy

Controversy: Which Pathologic Features of Nodal Involvement should Be an Indication for Adjuvant Groin Treatment?

Following IFL, patients with involved lymph nodes have been found to have groin failure rates of 24 % [54]. Adjuvant radiation to the groins and pelvis can significantly reduce the incidence of groin failures to 5 %, also resulting in a survival benefit [54]. The initial results of the GOG-37 study indicated benefit of adjuvant radiation for patients with two or more involved groin nodes. Subsequent subset and retrospective analyses have identified additional pathologic risk factors that are highly prognostic for groin recurrence including extracapsular extension [72–75] and macroscopic nodal involvement greater than 2–5 mm [58, 73, 76], even in a single node. By extrapolation, the higher risk of relapse with identified nodal

risk factors is considered rationale for adjuvant radiation to the groins by many clinicians. However, the role for adjuvant groin radiation for situations of extracapsular extension or macroscopic deposits in a single node remains controversial, as evidence of benefit is lacking at the present time.

Controversy: What Constitutes Optimal Adjuvant Therapy for Nodal Involvement?

A large variety of radiation techniques may be used to treat the inguinal lymph nodes, and no single technique has been widely accepted as optimal. Patient body habitus can have a significant influence on optimal choice of radiation technique to achieve adequate coverage of the groin nodes. Femoral vessel depth is a marker for groin node depth and may vary from 2 to 18 cm [67]. Therefore planning CT scans are useful to determine the treatment volume of interest that will adequately encompass the nodal bed. Large photon fields in an anterior-posterior orientation may achieve reliable coverage of the nodes at risk with a simple technique; however, more sophisticated techniques are being explored. Where inclusion of the femoral head or neck in the treatment volume is unavoidable, fracture or necrosis may occur in approximately 11 % of patient at 5 years, considered an acceptable risk compared to baseline for this age group [77].

Doses of adjuvant radiation are often chosen to reflect the possible burden of microscopic residual disease. Doses in the range of 45–50 Gy in fractions of 180 cGy are often used for microscopic nodal involvement, and higher doses of 54–56 Gy if macrometastatic lesions were identified, or 60 Gy if extranodal extension was present. There are no randomized data to evaluate the incremental benefit of chemotherapy. Conceptually, CRT may replace the need for RT dose escalation beyond doses of 56 Gy and minimize radiation-associated morbidity. GROINSS-V II study permits the addition of chemotherapy at the discretion of the physician [78].

Controversy: Does the Bilateral Groin Need to be Treated?

With involvement of only one groin after bilateral IFL, adjuvant nodal irradiation is often confined to the ipsilateral groin ± pelvis. As approximately 30 % of patients with pathologically positive groin nodes will also have pelvic lymph node involvement [53], radiation treatment encompassing a low pelvic field should be considered. The adjuvant radiation as delivered in the GOG-37 study, which resulted in improved survival due to decreased groin recurrence, encompassed bilateral groins in addition to the pelvis. Although ~25 % of patients with pathologic ipsilateral groin disease will also have contralateral disease and will therefore need consideration of bilateral adjuvant ingiono-femoral radiation; for patients with a pathologically negative, contralateral IFL, limiting the radiation portal to the involved side provides an opportunity to decrease the morbidity of adjuvant therapy and does not result in apparent excess contralateral groin failures [79].

Palliation and Recurrence

Palliation

For patients with the uncommon situation of presenting with distant metastatic disease, symptom palliation – which may consist of best supportive care or palliative radiotherapy – is clearly indicated. Data evaluating chemotherapy alone in advanced or metastatic vulvar cancer is sparse. However, response rates to conventional antineoplastic systemic therapy are poor, with a lack of response resulting in short survival (1–29 months) from progression of disease [80–82]. Palliative radiation, with its high response rates in the vulva, may be indicated for symptom control. In addition to disseminated metastatic disease, there are patients with locally advanced vulvar cancers in whom significantly advanced age and medical comorbidities preclude radical CRT for advanced vulvar carcinoma. A meta-analysis of 70 patients treated for vulvar cancer demonstrated a trend, although not a statistically significant difference, of an increased incidence of death from intercurrent disease or treatment complications during the study period in patients older than age 65 (11 %) compared with a younger cohort (3 %) receiving CRT [83]. In a large population, rates of intercurrent death were double those found in previous meta-analysis, reaching 20 % at 5 years [3].

Controversy: What Is Optimal Therapy When Patient-Related Factors Preclude Radical-Intent Treatment for Advanced Disease?

In addition to the complexity of primary vulva and nodal tumor factors, patient factors such as medical comorbidities and performance status should be considered in formulating a management plan for advanced vulvar cancers. However, it may be difficult to identify patients upfront who would be best served with a palliative approach, rather than curative intent therapy, due to tumor and/or patient factors. No useful data exists to guide the determination of therapy, and best clinical judgment is required to determine most appropriate therapy.

For patients in whom tolerance for treatment is questionable, management plans that can be transitioned to a radical intent based on tolerance and tumor response may provide the greatest flexibility in achieving the therapeutic goals of maximizing local and regional control, while simultaneously mini-

mizing treatment morbidity. Fractionation schemes such as 25 Gy in ten fractions can be repeated after a 2–3-week break for skin recovery and response assessment, allowing conversion of a palliative dose to an equivalent radical dose of radiation. Although there is no evidence in the literature for such a radiation schedule, information on improved local control with higher doses would support the potential for curative intent [26, 34]. Chemotherapy is not utilized in these circumstances, as incremental radiation dose to sites of disease involvement are likely to provide more effective control of disease with less toxicity than the addition of systemic chemotherapy.

Suggested fractionation schemes for palliative radiotherapy can include single fractions of 500–700 cGy which can be repeated at planned intervals or at recurrence of symptoms. More protracted schemes such as 25 Gy over ten fractions are also commonly utilized. No evidence of differential benefit of one palliative scheme over another is available to guide the choice of dose and fractionation for palliative radiation. Due to poor response rates [80, 81], no chemotherapy is typically used in this situation.

Recurrence

Treatment of recurrent disease is influenced not only by patient factors but also by sites of recurrence, prior treatment modalities received, and disease-free interval [84]. Local-regional sites dominate the pattern of disease recurrence and have much higher 5-year survival rates compared to regional or distant recurrences [24]. Five-year survival rates after regional or distant recurrence have been reported as 0–15 % [24, 85–90]. Groin node recurrences tend to occur earlier than vulvar recurrences, at a median interval of 7 months *versus* 36 months, and near the treated site, thus likely representing sites of persistent disease [90]. Groin node recurrences are typically not responsive to additional therapy and are ultimately lethal [91].

Controversy: Which Patients with Recurrent Vulvar Cancer Should Be Considered for Salvage Surgery Including Exenteration?

For patients in whom vulvar recurrences are not surgically resectable, management with CRT should be considered, unless patients have already received prior RT. In patients who have undergone previous RT/CRT treatment, options are limited to palliation with either symptom control measures only or with additional single fraction palliative radiotherapy, unless pelvic exenteration (PE) may be considered. Salvage surgery, including PE, with curative intent is indicated for a select group of patients with recurrence of vulvar cancer after antecedent radiotherapy, with no evidence of metastatic disease on imaging evaluation. In particular, central perineal or vaginal recurrences that involve the urethra, upper vagina, and/or rectum may be suitable for consideration of PE, if patient factors permit.

Controversy: What Is Optimal Management of the Groin in Recurrent Disease?

In patients without prior groin RT/CRT or full IFL, nodal management with vulvar recurrence is similar to the initial management of the groin. If the recurrence is well-lateralized, an ipsilateral IFL should be performed at the time of a wide local excision of the recurrent lesion, while bilateral IFL should be performed for recurrent lesions approximating the midline [92]. For patients who have undergone previous IFL, there may be a role for imaging in determining any benefit to repeat resection of the groin. While the chance of long-term disease-free survival after metachronous groin node metastases is extremely small, in a fit patient, post-op CRT may be used if multiple involved lymph nodes, macrometastasis, or extranodal extension are present [53, 72–76].

For patients who have received prior groin RT/CRT (either definitive or adjuvant), the opportunity to perform further surgical resection is limited by a high risk of debilitating wound complications [92]. Additional radical dose RT/CRT is not possible, nor is adequate adjuvant re-irradiation to the inguino-femoral region after an attempted IFL possible, as radiation tolerance doses within the field would be exceeded. Therefore, excisional procedures are avoided and palliative therapy is most appropriate. Palliative therapy may include symptom control only or additional single fraction palliative radiotherapy.

Conclusions and Future Directions

The controversies surrounding the staging and management of advanced vulvar cancer are difficult to address with randomized studies due to the relative rarity of the disease and variety of presentations. There is growing evidence for multimodality therapies and radiation dose escalation. Future studies to inform the management of vulvar cancer will require international cooperation, e.g., through the Gynecologic Cancer Inter Group, to accrue sufficient patients in order to resolve current controversies. Given the difficulty of obtaining Level 1 evidence, management decisions often rely on small retrospective series and the experience of a multidisciplinary team. To provide optimal management to patients with advanced vulvar cancer with the evidence currently available, individualized management plans should integrate the therapeutic advantages of the modalities available, tailored to the patient- and tumor-related factors in each situation. It is hoped that this summary will provide guidance in the complicated arena of advanced vulvar cancer.

Concluding Comments

- Individualized treatment plans should be developed in a multidisciplinary setting to utilize expert advice and currently available evidence.
- Surgery, chemotherapy, and radiation provide opportunities to maximize functional and oncologic outcomes in advanced vulvar malignancy.
- Multimodality therapies and radiation dose escalation for advanced vulvar malignancy require further evaluation through internationally cooperative randomized studies to resolve current controversies.

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Bowel Obstruction in Ovarian Cancer: To Operate or Not?

19

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Summary Points

- Initial management of an ovarian cancer patient newly diagnosed with malignant bowel obstruction
- Patient selection for surgical treatment
- Treatment options for nonsurgical medical therapy
- The role of total parenteral nutrition

Introduction

Advanced ovarian carcinoma is primarily a peritoneal disease that frequently involves the bowel mesenteries, peritoneal surfaces of liver and spleen, and the walls of the large and small bowels. Because of this unique pattern of spread, bowel obstruction is a common complication in patients with ovarian carcinoma [1]. Patients may present with bowel obstruction at the time of diagnosis, but it is mainly diagnosed in end-stage ovarian cancer, at which point it is the most common cause of death [2].

In this setting, bowel obstruction may be partial or complete and frequently involves multiple segments [3]. The pathophysiology of malignant bowel obstruction is in most cases multifactorial. Obstruction may be caused by occlusion of the intestinal lumen by an external mass, by tumor infiltrating the muscle layer causing reduced elasticity of the bowel, and/or by intestinal motility disorders secondary to infiltration of the myenteric nerve plexus [4]. Very rarely, paraneoplastic effects associated with autoantibodies have been described [5]. The presence of constipation with fecal impaction can further aggravate the problem.

Devoretsky et al. have described autopsy results of patients dying of ovarian cancer [6, 7]. They showed that direct extension of tumor into the bowel wall is a common finding. When bowel wall invasion was present, 71 % of these patients also manifested obstruction, whereas obstruction occurred in 30 % of patients with serosal involvement only. Importantly, bowel obstruction was multifocal in 76 % of the patients. When the obstruction was multifocal, it involved the small and large bowels in 79 % of cases, the small bowel alone in 13 %, and the large bowel exclusively in 8 %.

Apart from carcinomatous peritonitis and mechanical obstruction, adhesions due to one or more previous laparotomies are important causes of malignant bowel obstruction in ovarian cancer patients. Adhesions and other "benign" causes of malignant bowel obstruction (such as incarcerated hernia, chronic ischemia, and inflammatory bowel disease) occur in 3–48 % of cases [8]. Bowel obstruction may also be caused by radiation enteritis. However, the use of radiotherapy in ovarian cancer patients had decreased markedly in the past decades.

Bowel obstruction leads to proximal distention of the GI tract and the associated symptoms of nausea, vomiting, and abdominal pain. GI secretions and attempts at food intake lead to even greater distention and worsening of pain. The body initially appears to react with more secretions and peristalsis, propagating a vicious cycle [9, 10], which may finally lead to intestinal epithelial damage. Bowel obstruction may present acutely but typically presents with insidious onset and gradual worsening of symptoms over time.

Continuous abdominal pain caused by edema and inflammation of the bowel wall is the most constant feature and is

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present in approximately 90 % of the patients. Superimposed intestinal segmental activity to surmount the obstacle in the small or large bowel causes intermittent colic in approximately 75 % of the patients. When the large bowel is affected, the pain is generally less severe and deeper and occurs at longer intervals. Abdominal distension may be absent in high obstruction and when the bowel is "plastered" down by extensive mesenteric and omental spread. Vomiting develops early and in large amounts in duodenal and small bowel obstruction and later in large bowel obstruction.

Passage of bacteria or endotoxins across the bowel wall may occur with bowel obstruction with a risk of systemic infection [11]. Weakening of the bowel wall may eventually lead to perforation.

When a patient initially presents with symptoms suggestive of bowel obstruction, a thorough evaluation is performed including a complete physical examination, blood work, and imaging. Assessment of electrolytes and hydration and nutritional status is made and correction given as needed.

Radiological investigations should be performed to evaluate the extent of the disease and define the extent and level of the obstruction and the most likely cause. Abdominal radiography is taken in supine and standing positions when small bowel obstruction is suspected. Contrast radiography helps to evaluate dysmotility, to delineate partial obstruction, and to define the site(s) and extent of obstruction. Water-based contrast media such as Gastrografin are useful in such cases. It often provides excellent visualization of proximal obstructions, may reduce luminal edema, and may sometimes help in resolving partial obstructions. Abdominal computerized tomography is useful to evaluate the global extent of disease and to assist in the choice of surgical, endoscopic, or pharmacological palliative interventions for relief of the obstruction [8, 10, 12]. In some cases patients with bowel hypomotility secondary to disseminated intra-abdominal carcinomatosis lack the typical radiological signs of bowel obstruction and may demonstrate massive fecal loading instead.

The initial management should include restriction of oral intake, intravenous fluid repletion, antiemetics, and pain control, as needed, together with gastrointestinal decompression through a nasogastric tube if vomiting is copious and/or persistent [8, 10, 13].

Corticosteroids are sometimes given in order to reduce edema of the bowel wall and restore bowel passage. However, this approach has not been proven by randomized trials [14].

This phase of conservative management may continue for a variable period, usually several days. Some patients, especially those with partial obstruction, respond with restoration of bowel function and resolution of symptoms. Others do not and then a decision has to be made between surgical intervention and continued conservative medical management. This is a controversial area. In this chapter, surgical and non-surgical management will be discussed, and some of the arguments for and against each approach will be presented.

Controversies Surrounding the Role of Surgery for Bowel Obstruction

Surgical intervention is contemplated when the initial phase of conservative supportive treatment fails. It usually implies either adhesiolysis or the creation of an ileostomy or colostomy. Resection of the obstructing tumor or bypass surgery is rarely possible. The decision to operate is personalized, and sufficient time should be taken to discuss the operative risks and alternatives with the patient and her family to make sure the condition is understood and to determine their wishes. Consideration should be made as to whether the procedure is technically feasible, with an acceptable morbidity and mortality risk, and whether the procedure is likely to improve the patient's symptoms and quality of life [15].

Surgery for malignant bowel obstruction is technically challenging due to disease spread, ascites, and adhesions from previous surgery. The spread of disease in these patients is often underestimated on imaging, and diffuse peritoneal carcinomatosis and mesentery involvement are often found during surgery. As most patients with malignant bowel obstruction are in the advanced stages of their disease and have already usually received extensive chemotherapy, the aim of surgery is palliative and no surgical cytoreduction is performed. Kolomainen et al. [16] reported a median operative time of 85 min with a median blood loss of 500 ml. Bowel resection is required in approximately 50 % of cases, and in more than 60 % of patients a stoma is needed. Complications include fistula formation, anastomotic leaks, high-output stomas, wound infection or breakdown, abdominal collections or abscesses, and sepsis. Medical complications such as atrial fibrillation and pulmonary edema have also been reported.

The role of surgery in malignant bowel obstruction due to advanced gynecological cancer remains controversial. Published reports are mainly retrospective [1, 16–36] and reviews reflect expert opinion based on these retrospective data and the authors own experience and bias. Definitions of measured outcomes vary between studies and no uniformity exists. Length of hospital stay, survival, discharge on oral intake, time to re-obstruction, and more have all been used.

Surgery will not always achieve its goal of even short-term successful palliation. Surgical correction of the obstruction is not possible in 12–26 % of patients [17, 25, 27, 31]. Of note, patients who are short-term palliative surgery "successes" may eventually re-obstruct – the rate of re-obstruction is reported to be close to 10 %. Pothuri et al. [30] and Caprotti et al. [32] described repeat surgery for re-obstructed patients. Palliation was achieved in a minority of patients, and other methods of palliation should be sought in patients who fail initial surgery.

Postoperative morbidity is reported to be high. Complications (variously defined) are reported to occur in 15–64 % of patients [1, 16, 18, 19, 22, 23, 27, 29, 31, 33].

Functional outcomes of surgery, such as discharge home on regular or low-residue diet, ability to tolerate food, resumption of bowel function, and/or decrease of symptoms are often poorly defined and described. "Successful palliation" is described in 32–79 % of patients [16, 21, 23, 25, 27–29, 31, 33], but the reliability of these percentages is doubtful.

Survival after surgery for malignant bowel obstruction in patients with ovarian cancer is poor, reflecting the advanced stage of disease when these patients present and their often poor general condition. Postoperative mortality (unspecified or defined as mortality within 4–8 weeks after surgery) varies from 6 to 35 % and median survival after surgery from 2 to 8 months [1, 16–20, 22, 23, 25, 27–29, 31, 35].

What Are the Arguments for Nonsurgical Management of Bowel Obstruction?

Nonsurgical management includes palliative chemotherapy, stent placement for local obstruction, and palliation of symptoms, in particular vomiting and pain.

Ovarian cancer patients with bowel obstruction have usually already received extensive chemotherapy. The role of chemotherapy in these patients is therefore very limited [37]. Bryan et al. described the outcome of 17 patients with bowel obstruction receiving chemotherapy without surgery [33]. Seven of these patients had alleviation of intestinal obstruction. The best predictor of success was prior tumor sensitivity to platinum-based chemotherapeutic agents.

Local obstruction of duodenum or colon is very rare in patients with bowel obstruction due to ovarian cancer. In these rare patients, duodenal or colonic stents appear to be a useful option [10, 38–40].

Vomiting may be a major problem in refractory bowel obstruction. In these patients chronic proximal bowel decompression using a nasogastric tube or a percutaneous gastrostomy (PEG-)tube or treatment with octreotide or scopolamine butylbromide are viable options [8, 10, 13, 41]. Placement of a PEG-tube for decompression is possible in the majority of cases and safe [42–46]. It provides significant relief of vomiting. The effectiveness of octreotide for vomiting has been shown in several uncontrolled series (two of which used long-acting octreotide) in patients with bowel obstruction due to various tumors [47–55]. Therapeutic successes (often not well defined) were reported in 60–90 % of patients [56]. Three randomized trials compared octreotide to hyoscine butylbromide [57–59]; octreotide was found to be superior with regard to control of vomiting [51]. There have been no trials comparing proximal bowel decompression with treatment with octreotide. Octreotide may be combined with hyoscine butylbromide. Metoclopramide and haloperidol may be used if control of vomiting is not achieved with these compounds [10]. The use of metoclopramide is not recommended in the presence of complete bowel obstruction.

How Should Pain Associated with Bowel Obstruction Be Managed?

Treatment of pain due to bowel obstruction has not been systematically studied. For continuous pain, morphine is commonly used and for colicky pain hyoscine butylbromide [8–10, 60]. One trial reported that both hyoscine butylbromide and octreotide had favorable effects on both colicky and continuous pain [59].

Recently, a prospective study was published on the effect of a standardized protocol for nonsurgical treatment of malignant inoperable bowel obstruction [13]. Seventy-five consecutive patients (21 with ovarian cancer) with peritoneal carcinomatosis experiencing 80 episodes of bowel obstruction were treated with a three-stage protocol. Stage I involved a nasogastric tube (in the event of vomiting), parenteral rehydration, analgesics based on the WHO ladder, corticosteroids (methylprednisolone or equivalent), antisecretory drugs (hyoscine hydrobromide or hyoscine butylbromide s.c. or i.v.), and antiemetics (haloperidol or chlorpromazine s.c. or i.v.). If symptoms and signs persisted after 5 days, corticosteroids and antisecretory drugs were discontinued and octreotide was given for 3 days (stage II). If refractory nausea and vomiting persisted, octreotide was discontinued and a venting gastrostomy was performed (stage III).

The median survival was 31 days. Twenty-one patients had a survival of more than 2 months. Fifteen of these patients received chemotherapy. During stage I, obstruction relief was achieved in 25 cases and symptom control without obstruction relief in another 25 cases. Thirty patients proceeded to stage II and 14 to stage III. Ultimately, adequate symptom control was achieved in 90 % of cases. Fifty-eight of the obstruction episodes were controlled in 10 days or less.

What Factors Influence the Decision About Surgery or Conservative Management?

Ovarian cancer patients with bowel obstruction usually have advanced disease. They often have severe symptoms (in particular vomiting and pain) and low quality of life and are in poor general condition [15]. The main consideration for the choice of treatment should be its effect on quality of life. However, this has been poorly studied systematically [61]. Five small case series suggest an effect on symptoms and quality of life of both surgical and nonsurgical management [15, 60, 62–64].

Surgery for bowel obstruction in ovarian cancer patients is associated with a high degree of morbidity and mortality. However, some patients definitely benefit from surgery. The key issue, therefore, is optimal selection of those who are likely to improve after surgery and to refrain from surgery in patients who are unlikely to benefit.

A Cochrane Systematic Review aiming to compare the effectiveness and safety of palliative surgery and medical management for bowel obstruction in women with ovarian cancer [61] found only one low-quality, non-randomized study meeting the selected inclusion criteria [31]. This study analyzed retrospective data for 47 women who received either palliative surgery ($n=27$) or medical management with octreotide ($n=20$) and reported overall survival and perioperative mortality and morbidity. Quality of life was not assessed. Women with poor performance status were excluded from surgery. Despite serious morbidity and 22 % mortality, surgery was an independent prognostic factor for survival in multivariate analysis. However, this may have been due to selection of patients.

Many of the published uncontrolled series in ovarian cancer patients with bowel obstruction (including 31–98 patients per study, mostly treated surgically) have analyzed prognostic factors [16, 17, 19–22, 26, 34, 36]. The following were found to predict for worse survival: presence of ascites [16, 17, 20, 26], higher age [17, 20], poor nutritional status and/or low serum albumin [17, 19, 20], palpable tumor and/or advanced stage of disease [17, 19, 20], previous radiotherapy [17, 20], non-benign causes of obstruction [21, 36], short interval since last treatment [26], and nonsurgical treatment [21, 22, 31, 34]. However, in other studies, these factors were not found to be related to survival and multivariate analysis was rarely performed. Their value as predictive factors for the effect of surgery has not been proven.

Krebs and Goplerud [17] developed a prognostic index consisting of age, nutritional status, tumor spread, ascites, previous chemotherapy, and previous radiotherapy in 1983; this index was also found to be correlated to survival in two other more recent studies [24, 35].

One study looked at prognostic factors for "successful palliation" (defined as return home and relief of bowel obstruction for >2 months) [28]. Palpable abdominal and pelvic masses, large amount of ascites, multiple obstructive sites, and large preoperative weight loss predicted for a worse outcome.

What Is the Role of Total Parenteral Nutrition?

The role of total parenteral nutrition (TPN) in advanced ovarian cancer patients with bowel obstruction is controversial [37, 65–68]. Non-randomized trials suggest a survival advantage in patients receiving TPN [37, 67]. However, the survival difference is very likely due to patient selection rather than the effect of TPN.

TPN should only be considered for carefully selected patients with bowel obstruction due to ovarian cancer:

- As a temporary measure in patients treated surgically or in patients treated with first-line chemotherapy or second-line platinum-based chemotherapy >6 months after previous chemotherapy
- In the (very rare) patient with relatively isolated bowel obstruction (no organ dysfunction other than the gastrointestinal tract) treated nonsurgically, with a good performance status (WHO performance status 0 or 1) and an expected survival of >40–60 days [66, 68]

Conclusion and Future Directions

The impact of bowel obstruction in ovarian cancer patients on quality of life and survival is significant. Both surgical and nonsurgical treatment may significantly increase symptom control and improve quality of life. Survival for more than 3 months is rare, but may occur, particularly when chemotherapy is still an option.

All patients should receive a trial of conservative management, usually for at least a few days. During this period bowel passage may be restored. If not, then a decision has to be made about further management (surgical or nonsurgical).

Careful selection of patients for surgery is essential. The decision to operate should be a collaborative effort of surgeons, medical oncologists and/or palliative care physicians, based on clinical and radiological assessment. Arguments taken into account should include the treatment preference of the patient, performance status, age, nutritional status, the presence or absence of ascites, palpable mass and stage of the disease, local versus multiple obstructions, the site of obstruction (small intestine or colon), the possibility of benign causes (in particular adhesions), the interval since last treatment, and the possibilities for further chemotherapeutic treatment. It should be realized that the predictive value of these factors has not been proven and their relative weight is unknown.

There is an urgent need for randomized trials to assess the best treatment for malignant bowel obstruction [8, 69]. Ideally, these should be randomized controlled trials, comparing different approaches, using symptom control and quality of life as primary endpoints. This will aid to define effective therapy and identify selection criteria for specific treatments. Unfortunately, trials in patients with bowel obstruction prove to be difficult to perform [70], undoubtedly because of the poor condition of most patients and perhaps also due to reluctance of their doctors and nurses to include them in clinical research. Despite these impediments, malignant bowel obstruction has been selected as a target condition for research in palliative care [69]. Hopefully, this will result in methodologically sound and feasible studies in patients with malignant bowel obstruction, giving an evidence base for the management of a very difficult clinical problem.

Concluding Comments

- Randomized controlled trials are needed to define:
  - The optimal selection of patients for surgical treatment
  - The optimal management of symptoms (in particular vomiting and pain) of patients treated nonsurgically
  - The role of total parenteral nutrition
- The primary endpoint of these studies should be quality of life and management of symptoms

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Early Cervical Cancer: Can Fertility Be Safely Preserved?

20

Lukas Rob and Ruud Bekkers

Summary Points

Controversies exist about:

- Indication criteria for fertility-sparing surgery, regarding age, prior fertility history, and tumor characteristics.
- The need for sentinel lymph node mapping and intraoperative frozen section analysis with regard to full lymphadenectomy and/or local radical excision.
- The optimal surgical radicality of fertility-sparing procedures, regarding the radicality of the resection of paracervical tissue, and technique to reconstruct the neocervix.
- The optimal surgical procedure (vaginal, abdominal, robotic-assisted, or laparoscopic) radical trachelectomy with pelvic lymph node dissection.
- The indications, agents, dosing schedule, and final (oncological, pregnancy, and quality of life) results of neoadjuvant chemotherapy incorporated into the management of patients with cervical cancer wishing to preserve fertility.

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Introduction

Globally, more than 500,000 new invasive cervical cancer cases are diagnosed each year. The geographic distribution of cervical cancer is not uniform, however. In developed countries with a good public health infrastructure, screening of cervical cancer has led to an impressive reduction of incidence and mortality. Despite this positive trend, in 2004, 30,570 new invasive cervical cancer cases were diagnosed in 25 EU countries as well as an estimated 10,520 new cases of cervical cancer in the USA [1]. The majority of these invasive cervical cancer cases are diagnosed in early stages, and it is estimated that 25–40 % of them occur in women of reproductive age. For various reasons, many of these women may have postponed conception because delayed childbearing is a practice that has characterized the fertility behavior of women in almost all developed countries. For many decades, the only fertility-sparing surgical option for women who wished to retain reproductive function was conization in those women with less than 3 mm invasion (FIGO stage IA1 or GOG microinvasive definition without LVSI). Radical surgery and radiation therapy (less often) were the only options of treatment for women with cervical cancer of more than 3 mm invasion (FIGO stage IA2 or higher). Pregnancy was not possible after using either of these therapeutic approaches. This knowledge leads to the question of whether it is possible to preserve the uterus without increasing the risk of recurrence and to afford the opportunity for pregnancy.

Can Conservative Treatment with Preservation of Uterine Function Be Performed?

At the Society of Gynecologic Oncology Annual Meeting in 1994, Daniel Dargent and his group presented 8 years of experience with laparoscopic pelvic lymphadenectomy and vaginal radical trachelectomy (VRT) as a fertility-sparing therapy for early cervical cancer. This presentation led to the question of

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Table 20.1 Criteria for performing fertility-sparing surgery

Criteria for women	Strong desire to be fertile
	Appropriate age reflecting a reasonable chance for pregnancy – reproductive potential (40–45 years)
	Fully informed to allow a realistic choice to be made
Criteria for tumors	Tumor limited to the cervix (20 mm greatest dimension and less than half stromal invasion)[a]
	Neuroendocrine small cell cancer of the cervix is an exclusion criterion
	Negative pelvic lymph nodes
Criteria for centers	Extensive experience in fertility-sparing surgery with excellent quality control and follow-up

[a]Women with a tumor bigger than 2 cm are potential candidates for neoadjuvant chemotherapy or robotic-assisted radical abdominal trachelectomy

whether it is possible to perform less radical procedures than radical hysterectomy in order to preserve the uterus without increasing the risk of recurrence (oncological outcome), afford the opportunity for successful fertility (fertility outcome), and have a successful pregnancy leading to delivery of a healthy infant (pregnancy outcome). Shortly thereafter, a number of groups presented studies with laparoscopic lymphadenectomy and slightly modified VRT, mainly in tumors <2 cm in the biggest diameter. An abdominal fertility-sparing surgical procedure called abdominal radical trachelectomy (ART) was introduced into clinical practice in 1997 by an international group (Ungar, Del Priore, and Smith). This approach meets all requirements for standard radical resection of the parametrium in invasive cervical cancer and is currently substituted by complete robotic radical trachelectomy or complete laparoscopic trachelectomy. Complete antipodal procedures are those that reduce radicality of cervical and paracervical resection. In these procedures the laparoscopic lymphadenectomy (usually with sentinel lymph node detection) is followed by cone biopsy or simple trachelectomy. Some articles have been published on neoadjuvant chemotherapy (NAC) and fertility-sparing surgery in women with tumors larger than 2 cm. Finally, some groups advocate ART in those cases with a tumor diameter between 2 and 4 cm, claiming it is more radical than a VRT. The number of reported cases increased over the last 15 years, which resulted in many questions being answered but also raising new ones [2, 3]. This chapter reviews the advances in fertility-sparing surgery for early cervical cancer and presents current controversies that surround this field.

What Criteria Should Be Used to Select Patients for Fertility-Sparing Surgery?

Fertility-sparing surgery should be considered only in patients with a strong desire for future pregnancy. Preservation of the uterus for personal reasons in women who do not plan pregnancy is marked by controversy. Table 20.1 summarizes criteria for potential candidates for fertility-sparing surgery. In some centers, no clinical evidence of previously impaired fertility has also been included as a selection criterion. However, this is highly problematic because methods of assisted reproduction are widely used and most women are nulliparous. According to the literature, the number of nulliparous women is between 75 and 100 % [2], and in many of these women, fertility has not yet been tested. Specifying an upper age limit for fertility-sparing surgery is controversial, but most centers specify an upper age limit from 40 to 45 years. In a review of the literature, the average age of the youngest group was 27.6 years (range 24–31 years) and the oldest group had an average of 33 years (range 26–44 years). The average age in VRT patients was 31 years and in the ART patients 32 years [2, 3]. Patients need to be informed about preoperative examinations, type of surgery, alternative procedures, and late complications. In addition, patients need to be especially warned about the risk of premature delivery, that future pregnancy will be risky, and that they will have to reduce their normal lifestyle activities.

What Tumor Criteria Are Used to Select Patients for Fertility-Sparing Surgery?

Tumor Size or Volume

Tumor size or volume is an important criterion in most centers. Cone biopsy with exact diameter of the tumor is essential for accurate diagnosis of clinically undetectable early cervical cancer. Colposcopy and examination under anesthesia, which is the standard diagnostic procedure in clinically detected tumors, is important in assessing the ectocervical diameter as well as in excluding spread to the vagina. It is debatable whether tumor volume is the most important prognostic factor. In our opinion, preoperative tumor volumetry is the most important preoperative prognostic factor and even more important than tumor diameter. Magnetic resonance

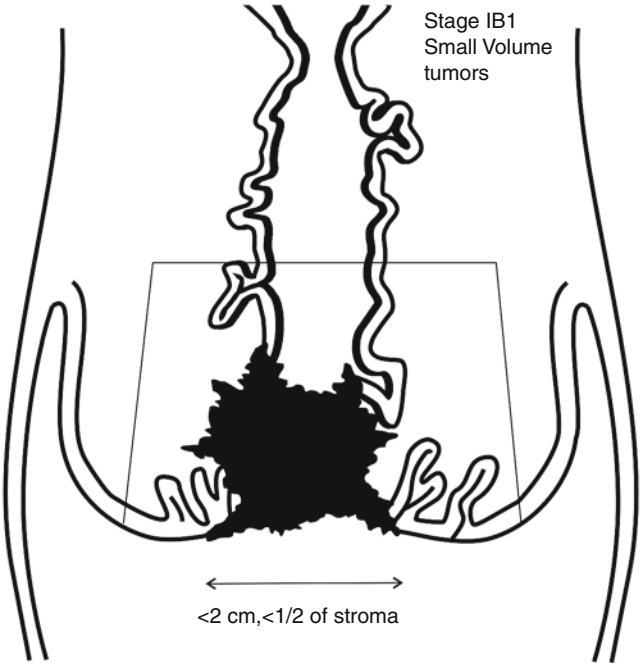

Fig. 20.1 Stage 1B1 small-volume tumors (less than 20 mm diameter, less than 10 mm deep in cone biopsy, or less than one-half of stromal invasion on volumetric MRI imaging)

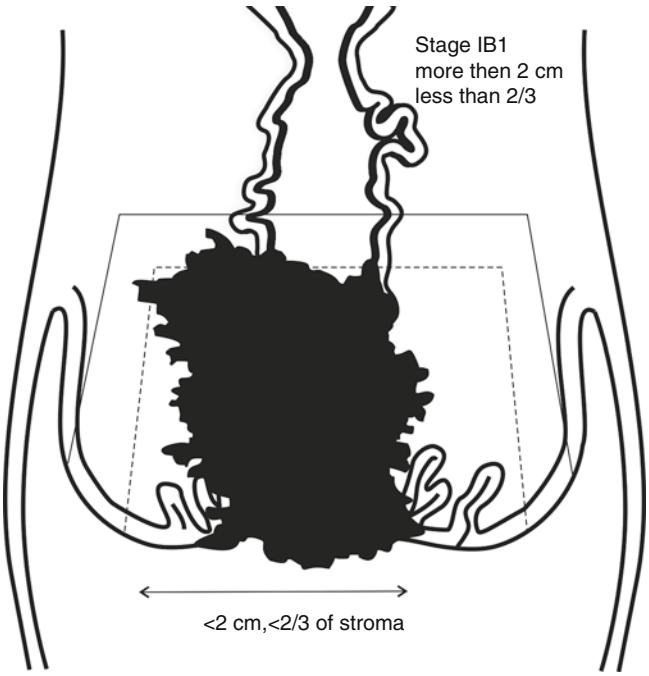

Fig. 20.2 Stage 1B1 tumor more than 20 mm or less than two-thirds of stromal invasion in volumetric MRI imaging

imaging (MRI) and ultrasonography (US) facilitate not only exact tumor measurement but also determine tumor volume (determination of the amount of cervical stroma infiltration and the amount of healthy stroma; determination of tumor growth in anteroposterior, craniocaudal, and transverse directions; or accurately determining residual disease after conization) as an important preoperative prognostic factor [4, 5]. Women with tumors less than 2 cm in largest diameter or stroma infiltration less than half of the stroma (Fig. 20.1) or invasion less than 10 mm (cone biopsy) have a significantly lower risk regarding involvement of the parametrium and pelvic lymph nodes [6–9]. Appropriate candidates for fertility-sparing surgery are patients with tumors smaller than 2 cm in diameter. The risks are higher for extrauterine spread and recurrence in IB1 tumors larger than 2 cm in diameter or infiltrating more than half of the stroma (Fig. 20.2) [10–12]. Fertility-sparing procedures that include the most radical abdominal or endoscopic (robotic or laparoscopic) trachelectomies are contentious, because it is necessary to have a 5–10 mm free margin, and at least 10 mm of healthy cervical stroma should remain after surgery to increase the probability of successful pregnancy. To reduce tumor volume some centers, use NAC in tumors bigger than 2 cm and infiltration more than half of the stroma. The oncological outcome of NAC followed by trachelectomy is unknown, and in our opinion this therapy should only be offered within the structure of an experimental protocol.

Histological Criteria

Most centers demand careful review of available histology obtained from biopsies taken outside the center. Preoperative biopsy gives information about some prognostic factors. Principal histopathologic prognostic factors are tumor size, depth of invasion, and histopathologic type. When tumor is clinically evident, a small biopsy is performed, but information about several risk factors is limited (tumor diameter, LVSI and VSI, or perineural involvement). It is important to exclude neuroendocrine carcinomas (both small cell and large cell), which are aggressive neoplasms that often occur in younger patients and are not suitable for fertility-sparing surgery [13]. LVSI and VSI are the most commonly discussed risk factors. Excluding tumors with LVSI from fertility-sparing protocols is controversial. In a recent study LVSI was present in about one-third of women who underwent fertility-sparing surgery [2]. It is necessary to standardize grading systems for LVSI or VSI. Women must be informed of these risk factors, as well as the risk of malignant extrauterine spread and the increased risk of recurrence in case of LVSI/VSI. In our own observation, LVSI/VSI at some distance from the primary tumor must be regarded as an intracervical metastasis, requiring a radical hysterectomy rather than fertility-sparing procedures, as recurrences in two patients have occurred (unpublished data). Other controversial prognostic factors are adenosquamous type, pattern of invasion, and perineural involvement. When

these risk factors are reviewed separately (including LVSI and VSI), they do not provide sufficient sensitivity in predicting tumor behavior in vivo, and therefore their use is still questionable [10].

Intraoperative Assessment and Adequate Margin in Trachelectomy and Pelvic Nodes

The first controversy concerns the importance of perioperative frozen section (FS) to identify an adequate trachelectomy margin of healthy stroma. A cross section of the superior portion of the separated cervix is sent for FS examination to assess the tumor-free status of the endocervical resection margin. A free endocervical margin of 5–10 mm is recommended by most centers. Otherwise, more of the endocervix needs to be removed, or the fertility-preserving surgery has to be abandoned. Perioperative assessment is not without its difficulties, especially in adenocarcinoma of the uterine cervix [14]. The majority of centers use this approach routinely, but when good preoperative volumetry is performed (MRI or US), it is possible to determine the exact size of stroma that is necessary to be removed and FS is supernumerary. Definitive histopathologic evaluation of cervical specimens is more precise than FS.

What Is the Role for Sentinel Lymph Node Detection and Frozen Section Analysis?

The second controversy pertains to the importance of using sentinel lymph node (SLN) detection and FSs of these nodes. The status of regional lymph nodes is the most important prognostic factor in patients with early cervical cancer. In patients with early cervical cancer, small lymph node metastases less than 10 mm are more common and not delineated as malignant by current preoperative imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET-CT). Perioperative assessment of regional lymph nodes can be done by repeated FS analysis, although this approach has been replaced in many centers by detection of SLNs. A number of studies have confirmed that sentinel lymph node mapping (SLNM) is feasible and highly accurate in predicting the status of regional lymph nodes in early cervical cancer [15, 16]. Presently, SLNs are detected by the application of blue dye and radioactive tracer (99mTc-radiocolloid). Good application technique and good timing of blue dye injection not only allow the identification of SLNs but also help identify and remove blue afferent lymphatic channels or nodes from the parametrium. A combination of both methods (radiocolloid and blue dye) is superior [17, 18]. These specimens are then forwarded separately to the histology laboratory for analysis.

Currently, the SLN procedure has been incorporated in fertility-sparing surgery management in many centers. Serial sections of SLNs increase the safety of fertility-sparing surgery, despite the optimal management of patients with postoperative detection of micrometastasis or isolated tumor cells (ITCs) still being debated [19, 20]. Some centers do not perform perioperative evaluation of lymph nodes if they are not suspicious and thus rely on final histopathology to determine their final decision. The intraoperative assessment of SLNs potentially modifies the surgical procedure and subsequent treatment management. Despite the obvious benefits of FS analysis for the patient (especially reduction of extent and number of operations), this technique has serious limitations. The intraoperative serial cutting of the entire SLN is not applicable because of the prolongation of operating time, technical limitations in processing frozen material, and loss of tissue for postoperative evaluation. FS allows for the reliable detection of clinically important metastases in lymph nodes (metastases bigger than 2 mm). The technique of FS fails only if micrometastases, less than 2 mm, and ITCs are diagnosed. Selection of SLN positive patients allows for perioperative modification of treatment; stop surgery and sends these patients for chemoradiotherapy protocols or more radical surgery. Final processing of the sentinel node biopsy has allowed more precise histopathologic evaluation of the "high-risk" nodes with serial sections and ultrastaging [19, 20]. The negative predictive value is thus higher than in ordinary lymph node assessment. Some centers have thus embarked on a two-step approach in fertility-sparing surgery. The initial step is laparoscopic SLN detection; then definitive histopathologic ultrastaging is requested and only in cases of negative SLNs is a fertility-sparing procedure planned.

Fertility-Sparing Options Current Procedures

Several fertility-sparing approaches are currently in use that vary according to the surgical radicality of the resection of paracervical tissue, the surgical technique of lymphadenectomy, and the techniques to reconstruct the neocervix. Figure 20.3 depicts the extent of possible resection of paracervical tissue and cervical resection.

Abdominal Radical Trachelectomy

A modification of abdominal radical hysterectomy, it does not need any special surgical training or instruments. The radicality of cervical and parametrial extirpation should be determined on an individual basis as in radical hysterectomy types B and C, with or without nerve-sparing surgery [21–24]. "Classical" ART provides standard radical resection of the parametrium with complete resection of the uterine vessels at their origin (Fig. 20.3). Modifications of ART with preservation

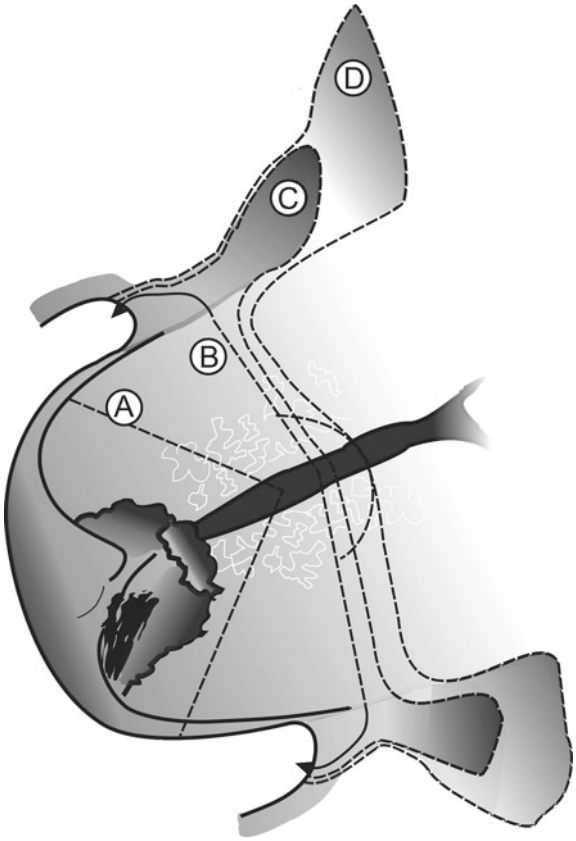

Fig. 20.3 (*A*) Cone biopsy, (*B*) simple trachelectomy, (*C*) radical vaginal trachelectomy, and (*D*) radical abdominal trachelectomy

of the uterine artery have been described elsewhere [21–24]. Progress in laparoscopic and robotic surgery in some centers has led to the performance of a total laparoscopic radical trachelectomy (TLRT) or total robotic radical trachelectomy (TRRT). Type B or C parametrial resection with or without nerve-sparing surgery is obtained by both TLRT and TRRT [25–27]. Suturing of the uterus and vagina together and formation of the neocervix, including catheterization of the neocervix, vary in different schools. Most centers prefer a permanent cerclage, whereas others perform cervical cerclage during pregnancy or do not perform cerclage at all.

Radical Vaginal Trachelectomy (RVT) (Dargent Operation)

This was developed as a modification of the Schauta-Stoeckel procedure. Growing progress in laparoscopic surgery enables us to perform laparoscopic pelvic lymphadenectomy and eventually parametrial lymph node dissection with or without SLN identification. The extent of laparoscopic surgery varies. The second phase of the procedure (vaginal phase) requires extensive experience in vaginal surgery. The vaginal phase starts with resection of the vaginal cuff and opening of the

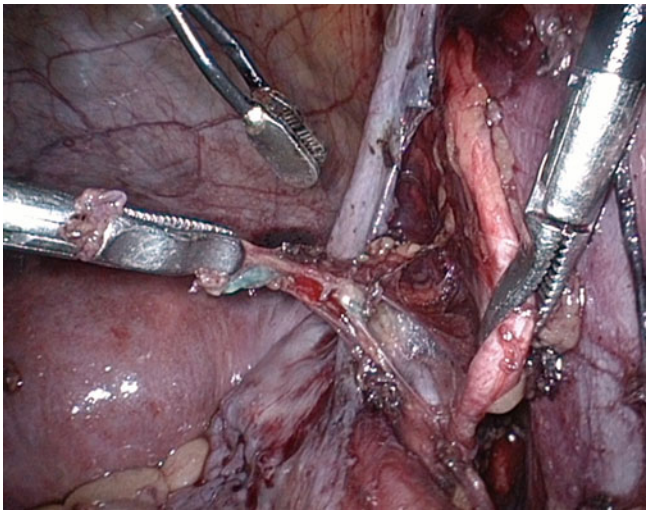

Fig. 20.4 Laparoscopic extirpation of parametrial blue lymphatic channel with a small lymph node

paravesical and pararectal spaces. Vaginally identifying and mobilizing the ureter is difficult but is necessary for safe resection of the parametria. Some centers use ureteral catheterization before surgery in order to easily identify and palpate the ureters. Radicality of the resection of the parametria is limited by the goal of preserving the uterine artery and only ligating the vaginal branch of this artery. The extent of resection of the parametrium is less radical (Fig. 20.3) than ART, TLRT, or TRRT procedures and can be partially replaced by laparoscopic extirpation of the lateral parts of the paracervix [27–32]. Most centers perform prophylactic cerclage with a nonabsorbable stitch, suturing the vaginal mucosa to the residual exocervical stroma. Finally, the vaginal mucosa is reapproximated to the new ectocervix using interrupted sutures.

Less Radical Fertility-Sparing Surgery: Laparoscopic Lymphadenectomy + Simple Trachelectomy or Large Cone Biopsy

A less radical surgery protocol was first described in 1999 by Rob et al. [33]. This less radical surgery involves two steps. The first step is laparoscopic SLN identification and FS of SLNs, extirpation of parametrial blue channels (Fig. 20.4), and eventually extirpation of blue lymph nodes in the medial part of the paracervix (the space between the obliterated umbilical artery and cervix). Pelvic lymphadenectomy is completed when sentinel nodes are confirmed negative on FS. After a 7-day interval, a second step involving reconization (stage IA1 with LVSI and stage IA2 tumors) or simple trachelectomy (stage IB1 tumors, less than 2 cm, less than 10 mm stromal invasion or less than one-half stromal invasion in NMR) is performed if the SLNs (ultramicrostaging) and other pelvic nodes (standard histopathologic evaluation) are negative. Retrospective studies

of parametrial involvement in small tumors with infiltration of less than 10 mm or less than half of the stroma, with negative pelvic lymph nodes, support less radical surgery without resection of paracervical tissue. The minimal risk of parametrial involvement in cases of negative SLNs has been confirmed by the Strnad et al. study, which was the first prospective study of its kind [34]. The injection of blue dye enables the removal of blue afferent lymphatic channels or nodes from the parametrium and decreases the risk of missing positive paracervical nodes. Simple trachelectomy involves amputation of the cervix with an incision 7–10 mm above the tumor, followed by removal of the endocervical channel using the loop electrosurgical excision procedure (LEEP) with a small (10 mm) loop electrode. Individual sutures to the outer edge created by the small loop reapproximate the vaginal edge circumferentially. Cervical cerclage is not performed and intracervical catheters are not used. This technique minimizes the risk of stenosis. Two-step management facilitated by ultramicrostaging of SLNs increases the safety of this conservative ("simple trachelectomy") procedure [35].

Maneo et al. and Raju et al. have published on less radical procedures that used pelvic lymphadenectomy and large cone biopsy in cervical cancer with small tumor volumes [36, 37] confirming the safety of less radical fertility-sparing procedures. Another less radical approach for preserving fertility is the use of chemoconization in patients with early cervical cancer, first described by Landoni et al. The first step in this approach is laparoscopic pelvic lymphadenectomy; in cases of negative nodes and tumors less than 2 cm, conization was performed to achieve clear margins of excision. When negative prognostic factors were present (LVSI, free margin less than 3 mm or deep stromal infiltration more than 10 mm), adjuvant chemotherapy (TIP or TEP regimen) was also given [38].

All these less radical fertility-sparing surgery techniques have yet to prove safe regarding oncological outcome. The absence of parametrial involvement in itself may indicate that removal of the parametrium is not necessary; however the local recurrence rate is the only valid outcome that matters. Rather than change policy based on circumstantial evidence of safety, one should embark on multicenter randomized trials to prove that less radical surgery is safe. Such a study will start in 2012 comparing radical hysterectomy with simple hysterectomy in patients with stage 1A2, or 1B1 < 2 cm and less than 50 % stromal invasion, cervical cancer patients (NCIC CTG CX.5/GCIG SHAPE trial). For fertility-sparing surgery, such a study is also feasible.

The second issue concerning less radical surgery is whether in patients with a relative low risk of lymph node metastasis it is feasible to omit complete pelvic lymph node dissection if the ultrastaging of the SLN is negative. Oncological safety data are missing so far, but a study in this area is surely worthwhile.

Neoadjuvant Chemotherapy and Fertility-Sparing Surgery

One of the limitations of fertility-preserving surgery occurs in patients with deep stromal invasion and tumors larger than 2 cm. Some centers use NAC with the aim of downstaging before radical hysterectomy. Few papers have examined NAC and fertility-sparing surgery using different approaches. The pioneering work on NAC and fertility-sparing surgery was presented by the Maneo group at the International Gynecological Cancer Society meeting in 2004. In 2008, the group updated their earlier findings [39]. The chemotherapy consisted of three courses of TIP or TEP every third week. After three courses of chemotherapy, patients underwent cold-knife cervical conization followed by complete pelvic lymphadenectomy. In a second approach, Plante et al. used the same chemotherapy protocol as in the Maneo study but surgery consisted of laparoscopic SLNM, pelvic lymphadenectomy, and radical vaginal trachelectomy [40]. The third approach is the Prague LAP-III protocol with dose dense chemotherapy. Only patients with tumors larger than 2 cm that have not infiltrated more than two-thirds of the stroma according to MRI volumetry were included. Three cycles of high-dose density NAC were used (cisplatin + ifosfamide or cisplatin + doxorubicin) at 10-day intervals. Surgery consisted of laparoscopic SLNM, removal of blue afferent lymphatic channels or nodes from the parametrium, pelvic lymphadenectomy, and vaginal simple trachelectomy [41]. NAC in fertility-sparing surgery in women with tumors larger than 20 mm in diameter with deep invasion is an experimental concept requiring verification, especially concerning oncological results. Also the type of chemotherapy that is the most effective with the least morbidity still needs to be elucidated. Pregnancy results are very good and NAC seems to have no impact on fertility [2].

Controversy: Extent of the Parametrectomy

The extent of the radical parametrectomy differs in various fertility-sparing procedures. A schematic illustration of the paracervical resection is shown in Figs. 20.3 and 20.5. VRT with laparoscopic pelvic lymphadenectomy is currently the gold standard for preserving fertility. The fundamental question is this: How many women after radical vaginal, abdominal, or robotic trachelectomy with a tumor ≤2 cm in the largest dimension and with negative SLNs have positive lymph nodes in the parametrium? Retrospective studies of parametrial involvement in small tumors with infiltration of <10 mm or less than half of the stroma that have not spread to the pelvic lymph nodes support the use of less radical surgery without resection of paracervical tissue. The risk of positivity in the paracervix is <1 %. The oncological results

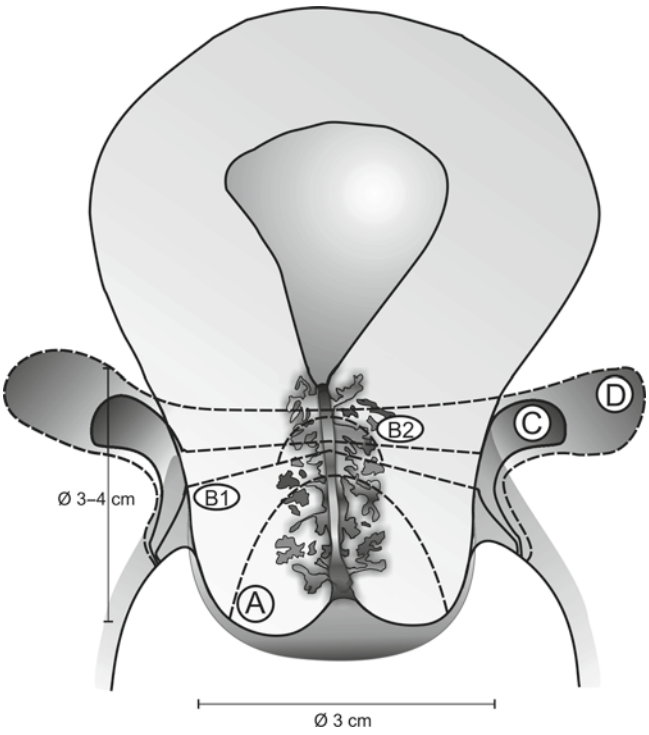

Fig. 20.5 (*A*) Cone biopsy, (*B*) simple trachelectomy, (*C*) radical vaginal trachelectomy, and (*D*) radical abdominal trachelectomy

are similar in ART, VRT, or less radical procedures in tumors of <2 cm and less than half of stromal invasion with negative pelvic nodes (recurrence is <4 % and death rate <2 %) [2]. Fertility-sparing procedures in this subgroup of tumors are now considered safe surgical procedures.

Controversy: Tumors >2 cm

A second controversy concerns what to do with tumors >2 cm with more than half stromal infiltration. Oncological outcomes in tumors >2 cm are not satisfactory. The recurrence rate in VRT is 20.8 %, which is nearly identical to the recurrence rate in ART [2, 3]. Downstaging by NAC is still an experimental procedure, and therefore more data are needed to verify its oncological safety. It is, however, clear that chemotherapy neither impacts fertility nor decreases the chance of pregnancy. Alternatively, some centers have embarked on ART in tumors of 2–4 cm with radical resection of the parametrium following the Hoeckel plains of dissection, but outcome data are lacking. At present, it is not feasible to declare any fertility-sparing procedure as oncologically safe in tumors over 2 cm in maximal diameter. Randomized studies comparing radical hysterectomy with fertility-sparing surgery are not ethical so large observational studies need to provide data on oncological outcomes.

Comparison Between Fertility and Delivery in Fertility-Sparing Procedures

In a recent *Lancet* paper, Rob et al. summarized the pregnancy results of VRT, ART, simple trachelectomy, and NAC [2]. The review evaluated the number of pregnant women, number of pregnancies, and number of deliveries in women in whom fertility was spared. Both less radical procedures (simple trachelectomy or cone biopsy with or without NAC) produced significantly better results. ART proved worse than the other procedures in all the parameters studied. The different pregnancy results need to be discussed in the context of the surgical procedures including a combination of the different factors (extent of extirpation of the cervix, technique of formation of the neocervix, and extent of resection of the paracervix). One factor that can further influence fertility is the higher risk of adhesions in open abdominal surgery as compared with laparoscopic techniques.

The extent of extirpation of the cervix leads to shortening of the cervix and a reduction of the amount and quality of cervical mucus. Today all techniques aim to save at least 1 cm of cervical stroma, but the extent of preservation directly influences pregnancy outcomes, making less radical fertility-sparing surgery attractive. The technique of formation of the neocervix may influence complications like cervical stenosis. Chronic irritation that is caused by a permanent cervical catheter can lead to cervical stenosis. Insertion of an intracervical catheter for 3 weeks is highly controversial because it can damage the endocervical epithelium of the remaining cervix. The risk of stenosis can be minimized by omitting the cerclage and insertion of an intracervical catheter.

The basic differences between the various techniques are the extent of resection of the parametria and the extent of disruption of the pelvic autonomic innervation by the inferior hypogastric plexus. The greater disruption of the innervation of the uterus and tube due to the larger resection of the paracervix is depicted schematically in Fig. 20.6. Radicality in the paracervix decreases the chance of spontaneous pregnancy and potentially increases the need for medically assisted reproduction.

The Future

Within the next few years, long-term data on outcomes in complete laparoscopic or robotic trachelectomy and pregnancy and oncological outcomes in ART and VRT and less radical procedures will eventuate. The authors hope that within the next few years it might be "standard" to use less aggressive surgical procedures than radical trachelectomy for women with low-risk early cervical cancer (squamous or adenocarcinoma <2 cm in diameter and <10 mm invasion). Less radical surgery will consist of the reduction of paracervical resection so that damage to the autonomic nerves, including branches of the inferior

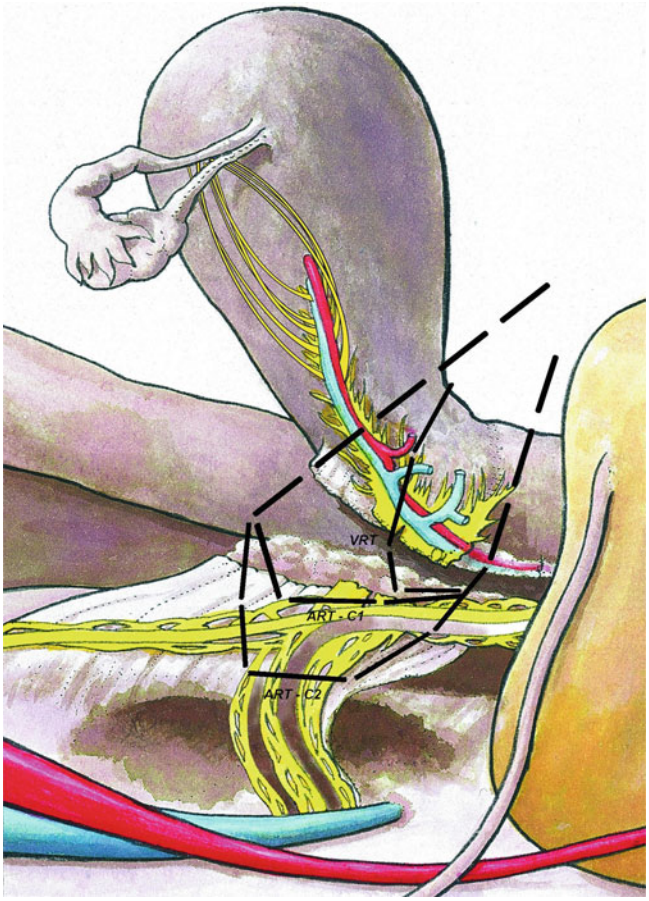

Fig. 20.6 Radical resection of the paracervix – disruption of the innervation of the uterus and tube. *ART* type C2 resection, *ART* type C1 resection, *VRT* vaginal radical trachelectomy

hypogastric plexus, will be minimized. Identification and extirpation of SLNs from the paracervix and pelvis will become important components of laparoscopic or robotic fertility-sparing surgery. Lymphadenectomy will be restricted to extirpation of SLNs in low-risk tumors. The use of prophylactic cerclage needs to be reevaluated as does the use of intracervical catheters. Finally the group of women that will most profit from NAC and/or fertility-sparing robotic-assisted, laparoscopic abdominal radical trachelectomy can be defined.

Concluding Comments

- Oncological safety and fertility/pregnancy outcomes in women treated with NAC before fertility-sparing surgery will need further study in patients with unfavorable tumors.
- The extent of radicality in fertility-sparing surgery in women with small tumors (<2 cm) must be studied.
- The need for a permanent cerclage and the use of intracervical catheters post-surgery must be evaluated.
- The impact of SLNM without further pelvic lymph node dissection on oncological outcome must be studied in women with small tumors.
- The most suitable NAC schedule must evolve with respect to tumor response and morbidity for women.

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What Is the Role of PET/CT in Gynecological Cancers?

21

Joanne Alfieri, Kailash Narayan, and Andrea Rockall

Summary Points

- Does the tailoring of radiation treatment fields according to findings on pretreatment ^{18}F-FDG-PET/CT improve survival outcomes in cervix cancer patients?
- Should preoperative ^{18}F-FDG-PET/CT be used as a tool to determine the extent of surgery in endometrial cancer?
- Will ^{18}F-FDG-PET/CT prove useful as an early response predictor after chemotherapy in ovarian cancer?

Introduction/Background

Positron emission tomography (PET) utilizes flouro-2-deoxy-D-glucose (FDG) as a tracer. The fluorine molecule (^{18}F) in FDG (^{18}F-FDG) is a radioactive isotope that emits a positron. The positron in turn annihilates with an electron releasing coincident photons detected by PET scanner [1]. Sterile non-pyrogenic FDG when injected intravenously is taken up by bodily tissues along with circulating normal glucose through a common glucose transport mechanism. According to the metabolic demands peculiar to the tissue type, some tissues such as brain and heart with high glucose turnover absorb more FDG (along with normal glucose). Thus, in a PET scan, a graded image of the glucose concentration in different tissues is observed. Malignant tumors have increased glucose metabolism due to increased hexokinase activity [2]. PET scans therefore provide circumstantial evidence for the presence of cancer by detecting accelerated glucose metabolic regions, where in the absence of cancer, concentration of glucose would have been low. PET images showing only metabolic activity without identifiable anatomical structures can be difficult to interpret. To overcome this limitation, PET/CT (computerized tomography using x-rays) is used [3]. A PET/CT uses PET images and a CT study on the same scanner without moving the patient. Functional and anatomical images from both studies are superimposed providing a better localization of the FDG in relation to anatomical structures.

Radiotracer uptake in patients can be assessed by several methods. These include visual inspection, the standardized uptake value (SUV), and the glucose metabolic rate. The SUV is the mathematical expression that is derived from tracer activity in the tissue in comparison with the injected radiotracer dose and patients weight. Generally the mean SUV of normal tissues such as the liver, lung, and bone marrow has a range of 0.5–2.5. Malignant tumors have an SUV of greater than 2.5–3.0. At the Peter MacCallum Cancer Centre (PMCC), we visually inspect the FDG-avid lesions and based on a given clinical situation label a lesion as neoplastic or benign. For example, in a cervix cancer patient with multiple FDG-avid pelvic nodes, a faint node with an SUV less than 2 will still be regarded as suspicious for metastatic disease. On the other hand, a mediastinal nodal mass with an SUV of greater than 3 in a pelvic and para-aortic node-negative cervix cancer patient will not be suspicious of metastatic disease. SUV is generally used as an adjunct to PET interpretation in equivocal lesions or in sequential follow-up of FDG-avid lesions.

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^{18}F-FDG-PET/CT can therefore be used as a noninvasive method to localize known or suspected primary gynecological cancers. With appropriate caution, it is also used in detecting metastatic lymph nodes and soft tissue lesions.

Although functional imaging such as ^{18}F-FDG-PET/CT is not currently included in the most recent gynecological malignancy guidelines [4, 5], PET/CT continues to play an increasing role in the diagnosis and treatment of gynecological malignancies in clinical practice. Several recent publications have emphasized the increasing importance of ^{18}F-FDG-PET/CT in various aspects surrounding the staging and treatment planning for gynecological malignancies [6–11]. This chapter will highlight the emerging role of $^{18F\text{-}FDG\text{-}PET}$/CT in the management of gynecological malignancies, with particular emphasis on the controversies surrounding its use.

Cervical Cancer

What Is the Role of PET/CT Staging of Cervical Cancer at Presentation?

The staging of cervix cancer has traditionally been clinical and remains that way. Besides inspection and palpation, the current accepted staging studies for cervix cancer under the FIGO staging system are colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and plain radiographs of the chest and skeleton [12].

Historically, FIGO stage of cervix cancer was the main prognostic indicator. Early-stage patients were treated either by surgery or radiotherapy, and locally advanced stages were treated by radiotherapy. Over the years, careful analyses of retrospective and prospective studies have brought to light several new prognostic factors other than FIGO stage. From histopathological examination of surgical specimens from early stage patients, the prognostic importance of tumor size, early parametrial invasion, and nodal metastasis has come to light. Later, due to the advent of CT, magnetic resonance imaging (MRI), and PET/CT, the significance of these prognostic factors was also studied in locally advanced cervix cancer patients where histological examination was not possible. This resulted in appropriate selection of patients for primary surgery, adjuvant radiotherapy, and definitive chemoradiotherapy. Although the surgical staging of cervix cancer patients paved the way towards understanding appropriate patient selection for the various treatment modalities, surgical lymph node exploration is invasive, is not without risks, and has been shown not to have a therapeutic value [13–15]. Due to associated morbidity and advances in imaging technology, surgical staging has largely been replaced by noninvasive PET/CT scanning.

Can PET/CT Usefully Determine the Extent of Primary Cervical Cancer?

In most cases, MRI is superior to PET/CT in evaluating local tumor due to better definition of soft tissues. Stage Ia tumors are usually diagnosed following an excisional biopsy. The vast majority of these tumors are cured by surgical resection. Occasionally ^{18}F-FDG-PET/CT has been performed following a biopsy to assess residual tumor, but the presence of post-biopsy inflammatory changes makes the interpretation of the PET/CT very difficult in this situation.

Clinically visible cervical tumors, stage IB1 and greater, are evaluable by ^{18}F-FDG-PET/CT. Smaller cervical tumors are occasionally missed, as the accumulation FDG in adjoining urinary bladder may mask these. Whereas MRI-based tumor dimensions correlate very well with histological measurements [16], PET/CT-based tumor volumes do not accurately correlate with MRI-based volumes [17]. Several investigators have studied the prognostic significance of various SUV levels in primary cervix tumors [18]. Unless any of these arbitrary SUV indices relate and indeed exceed in significance to several known prognostic factors, it is unlikely that measuring SUV will have any significant impact on clinical management of cervix cancer patients.

Imaging of Metastatic Lymph Nodes and Influence of ^{18}F-FDG-PET/CT on Radiation Treatment Fields

Following a landmark publication by Landoni et al. [19], it became clear that for patients with stages IB and IIA cervix cancer, either surgery or radiotherapy as the primary treatment was equally effective. However, following surgery, 54 and 84 % patients with tumor <4 and >4 cm, respectively, required postoperative radiotherapy due to associated histological poor prognostic features. The use of postoperative radiotherapy was associated with 28 % serious long-term effects compared with 12 % in those who were treated with radiotherapy alone. Presently, the most common indication for postoperative adjuvant radiotherapy in cervix cancer patients is the presence of metastatic lymph nodes. The undisputed clinical significance of ^{18}F-FDG-PET/CT is due to its ability to detect metastatic lymph nodes (Fig. 21.1a, b). In particular, the ability to detect tumor deposits in lymph nodes that are normal by size criteria has changed the management of cervix cancer patients. In addition to this, Fig. 21.1a, b also demonstrates how PET/CT can sometimes reveal synchronous primaries which need to be considered when an unusual pattern of FDG uptake is seen and emphasizes the importance of surveillance PET/CT (see discussion below).

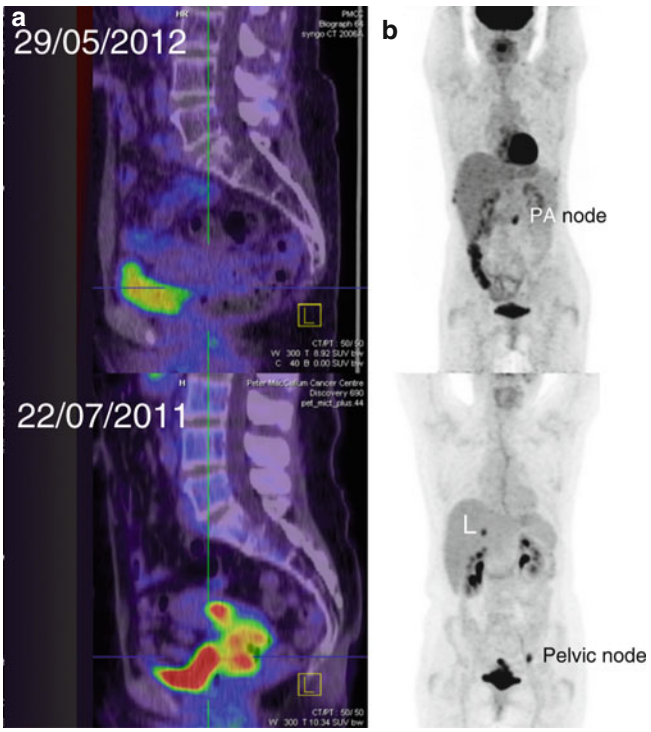

Fig. 21.1 Staging PET scan of a 53-year-old lady with a 5 cm carcinoma of cervix (FIGO stage IIb), performed on July 22, 2011. The PET scan demonstrates the cervical primary with extension into the uterus and an FDG-avid left external iliac lymph node. Interestingly, an FDG-avid 15 mm lesion was seen in the liver. This is an unusual pattern of uptake as liver metastases without extensive adenopathy are very rare in cervical cancer, and thus, biopsy was recommended (**a**). This patient was treated with chemoradiation for her cervix cancer until October 31, 2011. Interestingly, the liver lesion was biopsied on January 25, 2012, and was found to be an intrahepatic cholangiocarcinoma which was then surgically resected. Surveillance PET scan for this patient was performed on May 29, 2012 – 7 months after completing chemoradiation treatment for the cervical cancer. There was no residual uptake seen in the primary tumor and there was complete resolution of the left pelvic lymph node. A new FDG-avid nodal mass behind the left renal vein was present. There were no distant metastases. The activity seen in multiple right ribs is related to previous traumatic rib fractures (**b**)

The role of ^{18}F-FDG-PET/CT to provide disease mapping is emerging. However, nodal staging by ^{18}F-FDG-PET/CT prior to surgery is still controversial. Narayan et al. reported a lower sensitivity for para-aortic lymphadenopathy as compared to pelvic lymph nodes and confirmed that all histologically proven metastatic sites not visualized on ^{18}F-FDG-PET/CT were less than 1 cm in diameter [20].

Several papers have focused on presurgical detection of lymph nodes by ^{18}F-FDG-PET/CT; most find it to have a higher sensitivity, specificity, and positive predictive value than MR, missing only few micrometastases [21]. PET sensitivity for detecting malignant lymph nodes in cervix cancer varies according to the site of metastases and stage and volume of primary tumor. The sensitivity for ^{18}F-FDG-PET/CT in small-volume disease is still in question. Overall node-based sensitivity, specificity, PPV, NPV, and accuracy are 72, 99.7, 81, 99.5, and 99.3 %, respectively, increasing to 100, 99.6, 81, 100, and 99.6 %, respectively, if only nodes larger than 5 mm are considered [22]. PET/CT sensitivity for detecting pelvic and para-aortic nodes in advanced cervix cancer was 83 and 57–75 %, respectively [20, 23]. In patients with early-stage disease and small tumors who did not have any enlarged nodes on MRI, PET/CT detected only 10 % metastases when compared with final surgical examination [24]. Interestingly, one group has found that SUV_{max} was a predictive biomarker of lymph node status at diagnosis, persistent disease after treatment, risk of pelvic recurrence and/or distant metastasis, and overall survival to a greater extent than patient and tumor-related factors [25]. ^{18}F-FDG-PET/CT may at times also help clarify uncertainties with respect to possible metastatic lesions discovered on other radiological examinations or discover completely new foci of disease. As such, it aids clinical decision-making with respect to curative versus palliative treatment intent.

How should this information be used in clinical practice? While not trying to change the FIGO staging system, we clearly need to divide early-stage patients who are presently treated by primary surgery into three categories. The first category of patients who have stage I, small-volume disease is those deemed suitable for treatment using either cone biopsy or trachelectomy. PET/CT in this category of patients is unlikely to detect positive nodes. Sentinel lymph node biopsy may be useful in this situation in limiting the extent of node dissection for those patients planned to undergo lymphadenectomy.

The second category of patients would consist of stages IB1 and IIA1 patients. PET/CT will divide this category of patients into two groups – a larger group with PET-negative nodes and a smaller group with PET-positive nodes. PET node-negative patients can be treated with primary surgery, provided lymphadenectomy is performed before hysterectomy and suspicious nodes are sent for frozen section histopathology. If metastatic deposits are found in the frozen section, hysterectomy should then be aborted and the patient sent for treatment with primary chemoradiation. The planned surgery should be carried out in pathological node-negative patients. The aim is to avoid dual modality treatment toxicity in node-positive patients. In our center, in FIGO stage IB1 patients, initially selected for primary surgical treatment, the failure rate was 14 % ($n=83$) in those patients with PET-negative nodes confirmed to be negative histologically on subsequent radical hysterectomy, 19 % ($n=21$) in those patients for whom hysterectomy was aborted and who were then treated with chemoradiation because of pathologically positive nodes, and 34 % ($n=35$) in those patients who did not undergo staging PET/CT and underwent radical hysterectomy and lymphadenectomy.

The third category would consist of all patients found to have a clinical tumor diameter larger than 4 cm (IB2, IIA2, and higher stages). All these patients should have tailored concurrent chemoradiation with a planned nodal boost based on the PET/CT findings. In 206 cervical cancer patients staged by PET/CT, stage FIGO IB1 with positive nodes or any IB2–IVA, 5-year relapse-free survival rates were 81 and 62 % for PET node-negative and node-positive patients, respectively [26].

The standard of care for cervix cancers of FIGO stages IB2–IVA is concurrent chemoradiotherapy. The use of ^{18}F-FDG-PET/CT has been adopted by centers with access to this resource to alter the radiation treatment fields and doses used. For example, Grigsby et al. identified PET/CT-positive para-aortic lymph nodes as the most significant independent prognostic factor for progression-free survival. Extending the radiation field to include PET/CT-positive para-aortic lymph nodes has become common practice [11]. Individualized treatment with dose intensification to FDG-avid lymph nodes has also been shown to be of value [27].

The question is whether the use of PET/CT appropriately triages patients into the correct treatment modality producing the least treatment-related toxicities and whether such a triage actually improves survival [28]. In a study of 414 stages IB–IVA, cervix cancer patients treated with chemoradiation at PMCC, between 1996 and 2008, 100 had nodal staging performed using laparoscopic nodal sampling (LAP), 241 had nodal staging using PET, and 73 had only MRI for assessment of nodal status. The failure at any site was similar in all groups: 38 % for LAP, 35 % for PET, and 33 % for MRI-staged patients [15]. There were no significant differences in survival between the groups either. This may be due to the manner in which radiotherapy treatment is delivered and to the propensity for node-positive patients to relapse systemically [26]. Most of the positive nodes in advanced-stage cervix cancer can be easily detected by MRI or CT scan because they are greater than 1 cm diameter in the short axis. During chemoradiation treatment, these enlarged nodes can be boosted an additional 6–10 Gy. Although subcentimetric lymph nodes may still harbor cancer cells, small-volume disease can be controlled with the whole-pelvic radiotherapy and concurrent (radio-sensitizing) chemotherapy. A recent analysis by Narayan et al. [26] revealed that nodal status on PET was a major predictor of outcome and superior to FIGO staging. In locoregionally advanced cervix cancer patients, the incidence of PET-positive nodes at the level of the common iliac and para-aortic regions combined was 21 % [26], similar to the 24.3 % in surgically staged patients [13]. However, knowing the nodal status and modifying the radiation field to extend to the top of the para-aortic nodal chain still results in 2–5-year DFS of 18–19.4 % [11, 29]. Staging cervix cancer patients with ^{18}F-FDG-PET/CT currently allows the allocation of treatment modality appropriately. However, whether PET/CT-based individualized radiation treatment plans improve survival still requires further study.

Evaluation of Response to Therapy Post-completion

Grigsby et al. studied post-therapy completion ^{18}F-FDG-PET/CT. They showed that a complete metabolic response led to a 5-year cause-specific survival (CSS) of 80 % while patients with abnormal uptake had a 5-year CSS of only 32 % and all patients with abnormal uptake outside the irradiated field died within 5 years [30]. Similarly, their more recent publications reported a 3-year PFS 78 % for complete response, 33 % for partial response, and 0 % for progressive disease [31, 32].

In general early salvage surgery should be avoided whenever possible. Although this may sound counterintuitive, the following data must be taken into consideration. Ninety-six patients with FIGO stages IB2–IVA cervix cancer had a surveillance MRI and PET/CT performed at 4–6 weeks after completing neoadjuvant chemoradiation and immediately prior to their completion surgery [33]. Results were compared with the pathological specimen as the reference standard. There was no difference in the accuracy values between the two imaging modalities. Neither MRI nor PET/CT accurately detected residual disease. Sinus histiocytosis was the most frequent cause for a false positive on PET/CT. The presence of scattered viable cells among sclerotic lymph nodes resulted in a false-negative PET/CT scan. Between 1985 and 1994, 421 women with stage Ib or II cervical carcinoma were treated by surgery in combination with irradiation. Each underwent a radical hysterectomy with systematic pelvic and para-aortic lymphadenectomy. The frequency of para-aortic metastases was 8 % [34]. The same group treated 73, FIGO stage IB or II patients between 1998 and 2004, with standard, curative, chemoradiotherapy and intracavitary brachytherapy. A completion surgery was performed subsequently with at least para-aortic lymphadenectomy. To their surprise, 17 % of their patients had positive para-aortic nodes, more than double the rate of para-aortic lymph node positivity found in the previous study. In other words, increased metastatic disease appeared during radiotherapy treatment [35].

At the PMCC, we have noticed both these phenomena in radically treated cervix cancer patients, whose follow-up data have been prospectively recorded. There have been several cases of persistent uptake at the primary and/or nodal sites on surveillance PET/CT performed 4–5 months following the completion of their chemoradiotherapy which either resolves on subsequent PET/CT scan 3 months later or progresses to reveal multisite failure. In either case, salvage

surgery performed at the first time point would have been either unnecessary or futile.

However, salvage curative surgical treatment is done if isolated disease (usually para-aortic lymph node or rarely, persistence at the primary site) is still present at the second follow-up PET/CT scan. This salvage is usually successful. Likewise, we have noticed that as many as 24 % of patients fail in the para-aortic region following careful pretreatment PET/CT staging and curative chemoradiotherapy. In our institution, these two observations have led to the scheduling of the surveillance PET/CT at 4–6 months after the completion of chemoradiotherapy. Siva et al. found that surveillance ^{18}F-FDG-PET/CT is predictive of survival; an overall survival rate of 95 % is observed in those patients who have a complete metabolic response at this stage [36]. The results from this study suggest that resource-intensive follow-up can be eliminated for those patients achieving a complete metabolic response on a surveillance ^{18}F-FDG-PET/CT. The value for long-term follow-up lies in the capability to diagnose and treat late radiation toxicities or to reassure anxious patients, as routine follow-up in asymptomatic patients does not lead to early detection [37].

Detection of Recurrent Disease During Follow-Up

It has been shown that ^{18}F-FDG-PET/CT can detect recurrent disease earlier than structural imaging [38]. This being said, it is important to reiterate that isolated locoregional or nodal failures are extremely uncommon and in the order of approximately 2 % [27]. With respect to recurrent cervical cancer, ^{18}F-FDG-PET/CT results in a change in management in 23.5–65.5 % of patients [39, 40].

Conclusion

^{18}F-FDG-PET/CT is a useful tool that can help clinicians improve the selection of patients for curative treatments and exclude those patients who will not benefit from resource-intensive follow-up. At PMCC, surgical lymph node mapping, with the goal of informing the radiotherapy treatment fields, has largely been abandoned. PMCC has given up laparoscopic staging except for those patients who will be treated surgically. Those patients undergo a two-stage procedure: laparascopic or extraperitoneal lymph node lymph node dissection followed by radical hysterectomy if the lymph nodes are negative on histopathology.

Unanswered questions remain about the role of $^{18F\text{-}FDG\text{-}PET}$/CT in primary tumor staging. Its role in lymph node staging of advanced cervical cancer is established, but the contribution of PET/CT imaging to detect lymph nodes in small-volume primary disease in early-stage patients remains unclear and requires further study.

The role of ^{18}F-FDG-PET/CT in establishing relapse has been confirmed, and this technology can have a major impact on clinical decision-making and patient management. Although the optimal timing for surveillance ^{18}F-FDG-PET/CT is not established, it is important to note that false-positive results can occur in the primary tumor on surveillance ^{18}F-FDG-PET/CT performed at 3 months. Therefore, in order to avoid acting on a false-positive result with surgical salvage therapy, it is recommended to repeat metabolic imaging 3 months later. Furthermore, patients whose surveillance ^{18}F-FDG-PET/CT reveals positivity in the pelvic or para-aortic lymph nodes should also undergo repeat metabolic imaging 3 months later to ensure that the failure is indeed isolated, prior to commencing local salvage therapy. Repeat ^{18}F-FDG-PET/CT will reveal distant metastases in the majority of patients with an initial seemingly isolated nodal failure and prevent futile local therapy.

Endometrial Cancer

Endometrial cancer is the most common gynecological cancer in the developed world. Most cases are detected at an early stage and have a favorable prognosis, as they are cured with surgery. Advanced-stage disease, on the other hand, has a high relapse rate and an increased risk of distant metastases. Those with a high risk of recurrence may benefit from adjuvant treatment. These high-risk features are best evaluated by histological examination of the pathological specimen. Therefore, the currently accepted staging method for endometrial cancer is surgical [12]. Preoperative assessment for distant disease is most often based on imaging of the chest with x-ray or CT and imaging of the abdomen and pelvis by CT or MRI. It has been shown that evaluation of nodal disease and micrometastases with these methods is suboptimal [41]. A noninvasive method of providing accurate information about nodal and distant spread would be helpful in determining appropriate management and may help to avoid unnecessary surgical procedures for these patients.

Does ^{18}F-FDG-PET/CT Staging Have a Role in the Detection of Lymph Node Involvement and Metastases at Presentation?

The assessment of ^{18}F-FDG-PET/CT in the preoperative evaluation of endometrial cancer patients is not as well developed as its role in cervical cancer. Less than 20 % of women with endometrial cancer have lymph node metastases at presentation. One of the main controversies

surrounding the management of endometrial cancers remains the selection of patients who may benefit from lymphadenectomy. The general consensus in the literature is that $^{18F\text{-}FDG\text{-}PET}$/CT is only moderately sensitive (53 %) in predicting lymph node metastases and cannot replace surgical lymphadenectomy in the staging of endometrial cancer patients [41]. Despite this, staging by PET/CT may be a good option for those patients who are poor surgical candidates as it is superior to other imaging techniques in detecting the extent of primary tumor and metastatic lymph nodes, with specificity and accuracy of 99.6 and 97.8 %, respectively, for node detection [41, 42]. It remains a good alternative for evaluating lymph nodes in high-risk patients in whom lymphadenectomy was not performed. In the series by Park et al., 53 patients underwent preoperative imaging with $^{18F\text{-}FDG\text{-}PET}$/CT and MRI. The authors concluded that the value of PET/CT came from its high sensitivity for detecting distant metastases (100 %) and its high negative predictive value in predicting LN metastasis (96.6 %) [42]. Signorelli et al. examined the diagnostic accuracy of ^{18}F-FDG-PET/CT in the detection of nodal metastases in patients with high-risk endometrial cancer. Based on the negative predictive value and accuracy of 97.2 and 96.8 %, respectively, the authors concluded that ^{18}F-FDG-PET/CT is an accurate method for the presurgical evaluation of pelvic nodes metastases [43]. The high negative predictive value may be useful in selecting only those patients who may benefit most from lymphadenectomy, minimizing operative and surgical complications.

Does PET/CT Have a Role in Detecting Recurrent Disease During Follow-Up?

The overall risk of endometrial cancer recurrence is 13 %. Sixty percent of all recurrences are distant metastases. Between 70 and 100 % of recurrences occur within 3–5 years of the primary treatment. The fact that only approximately 1 % of recurrences are asymptomatic is based on the retrospective surveillance studies assessing for recurrence with physical exam, CA 125, chest x-ray, Papanicolaou test, abdominal ultrasound, and CT scan of the abdomen and pelvis [44]. The National Comprehensive Cancer Network (NCCN) guidelines recommend physical examination every 3–6 months for 2 years and every 6 months or annually thereafter along with education regarding symptoms suggestive of recurrence. They also state that CA 125 is optional and classify the performance of vaginal cytology and annual CXR as category 2B, that is, based on lower level evidence. They also suggest that CT/MRI should only be performed when clinically indicated [45]. Despite these guidelines, there is no clear consensus among clinicians as to how to follow the patients at highest risk of recurrent disease [46, 47]. Salvage rates among patients who recur remain controversial and vary between 10 and 38 % [48, 49]. There is an exception for patients with vaginal recurrences who were not previously irradiated where the salvage rate is high [50]. It is well known, however, that distant relapse is associated with a poor outcome [51]. A reliable tool for the detection of salvageable recurrent disease may improve survival and decrease morbidity secondary to the recurrence [44].

^{18}F-FDG-PET/CT has been shown to improve the management of recurrent or metastatic disease in both endometrial adenocarcinomas and uterine sarcomas and is especially useful in the detection of peritoneal spread of disease [49, 52–54]. PET/CT in the setting of recurrent endometrial cancer has been found to have a sensitivity, specificity, and accuracy of 91–100, 83–100, and 92–96 %, respectively. The information obtained from the ^{18}F-FDG-PET/CT influenced clinical management in 22–42 % of cases [49, 55–57]. It has also been reported that the 2-year progression-free survival was 100 % in the patients with a negative post-therapy surveillance PET/CT versus 33.7 % in those patients with a positive PET/CT scan [49]. The limitations of PET/CT were a false-negative rate of 5–10 % and the moderate spatial resolution of current systems of 4–6 mm [57].

The superior value of ^{18}F-FDG-PET/CT has been demonstrated clearly in the detection of peritoneal spread in patients with uterine sarcoma, where ultrasound and CT scans failed to detect any disease. FDG-PET was also superior in the detection of extra-pelvic disease, the most common form of recurrence in this disease [52–54].

Ovarian Cancer

Ovarian cancer has a high mortality rate and there is an urgent need to improve patient outcome. Earlier detection of disease, together with improvements in precision management of each patient, including optimal primary surgical treatment, optimal chemotherapy, and early detection and treatment of recurrence are all areas that may hold potential to improve patient outcome. Imaging may have an important role to play in contributing in each of these areas. The role of ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are well established in the management pathway. There remains debate concerning the appropriate use of ^{18}F-FDG-PET/CT. In this section, the literature on the use of ^{18}F-FDG-PET and ^{18}F-FDG-PET/CT in ovarian cancer will be reviewed, highlighting controversial areas.

Early Detection of Disease

Ultrasound is the initial imaging modality for the detection of ovarian cancer. MRI plays important role in the

characterization of adnexal masses that are indeterminate on ultrasound, having a high sensitivity and specificity [58]. However, a number of cases remain indeterminate following MRI. ^{18}F-FDG-PET/CT has been used to detect malignancy in adnexal masses and some studies report a higher specificity when compared to transvaginal ultrasound or CT [59–62]. In premenopausal women, ^{18}F-FDG-PET/CT is hampered by physiological uptake in normal ovaries, which confounds interpretation. FDG uptake in postmenopausal ovaries is abnormal but it is known that some benign ovarian lesions, such as cystadenomas and dermoid cysts, take up FDG, potentially causing false-positive results. Conversely, some ovarian borderline or low-grade invasive malignancies demonstrate relatively low FDG uptake [63]. Nonetheless, a recent study by Nam et al. showed a higher accuracy for ^{18}F-FDG-PET/CT than pelvic U/S, CT abdomen and pelvis, or pelvic MR in differentiating between malignant/borderline and benign ovarian lesions [62]. They also reported finding unexpected extra-abdominal nodal disease in 15 of the 95 patients with ovarian cancer as well as another primary malignancy in 5 patients.

Staging of Primary Cancer

In patients with a high likelihood of ovarian cancer, based on the initial investigations, CT is widely used to determine the extent of disease in order to determine whether primary surgical cytoreduction can be achieved [64]. However, there are well-recognized limitations of CT in this setting [65].

If integrated ^{18}F-FDG-PET/CT is used in the initial staging, using diagnostic CT scan with intravenous contrast administration, the number of sites of disease detected may increase [62]. However, it is unclear whether this would change decision-making in treatment planning. Small-volume disease may not be within the resolution of PET or PET/CT. However, unsuspected sites of disease beyond the abdomen may be identified, potentially changing management from primary surgery to neoadjuvant chemotherapy. In addition, there is the possible benefit of using quantitative SUV data for the early evaluation of response in patients who then undergo neoadjuvant chemotherapy (see section below).

Recent studies that evaluated the staging accuracy of ^{18}F-FDG-PET/CT have reported high sensitivity, specificity, and accuracy for detecting the extent and distribution of disease when compared to surgical and histopathological reference standards [66, 67]. In a large prospective study of 179 patients, the results of PET imaging provided some predictors of incomplete cytoreduction [68]. However, the authors state that PET findings alone should not be used to withhold cytoreductive surgery [68]. Thus, the role of PET in preoperative decision-making is not fully established.

What Is the Role of FDG-PET/CT in Evaluating Disease Prior to Starting Chemotherapy and Assessing Tumor Response?

There may be a role for using ^{18}F-FDG-PET/CT as a baseline imaging technique prior to starting chemotherapy. This could be used in two different settings:

1. Detection of residual disease following cytoreductive surgery. In these cases, knowledge of the extent of disease prior to starting chemotherapy could be important in accurate assessment of response. It is known that even in patients thought to have complete or optimal cytoreductive surgery, postoperative CT is discordant in approximately 50 % patients, with CT demonstrating unsuspected residual disease [69]. It is possible that early postoperative ^{18}F-FDG-PET/CT may provide a more accurate evaluation and thus allow better assessment of response to chemotherapy. Thus, it could be argued that patients should undergo PET/CT at baseline, before the start of chemotherapy, even in those patients considered to have had optimal tumor debulking at surgery.
2. In patients that will be treated with neoadjuvant chemotherapy, evaluation of disease status with ^{18}F-FDG-PET/CT may allow more complete nonsurgical staging than CT alone and provides baseline metabolic data for early evaluation of response to treatment.

There is evidence to support ^{18}F-FDG-PET/CT as an early response predictor (Fig. 21.2a, b). In a prospective study of 33 patients with untreated ovarian cancer being treated with three cycles of neoadjuvant chemotherapy followed by surgery, Avril et al. evaluated sequential SUV measurements from FDG-PET, as well as clinical, CA125 and histological response indicators before and after chemotherapy [70]. They found a significant correlation between metabolic response and overall survival when comparing baseline SUV measures to those after the first ($p=0.008$) and the third ($p=0.005$) cycles of chemotherapy. No correlation was found between clinical and CA125 markers of response and overall survival, and only a weak correlation was found with histological markers of response ($p=0.09$).

^{18}F-FDG-PET/CT has also been suggested as an alternative to second-look laparotomy (SLL) at the end of treatment, with reported accuracies of 77–86 % [71, 72]. However, this would only be of value in cases where SLL was being considered, which is currently not the surgical norm.

Detection of Recurrent Disease

^{18}F-FDG-PET/CT has been reported to detect recurrent disease in patients with CA125 relapse and negative CT, albeit with a high rate (59.3 %) of false-negative findings

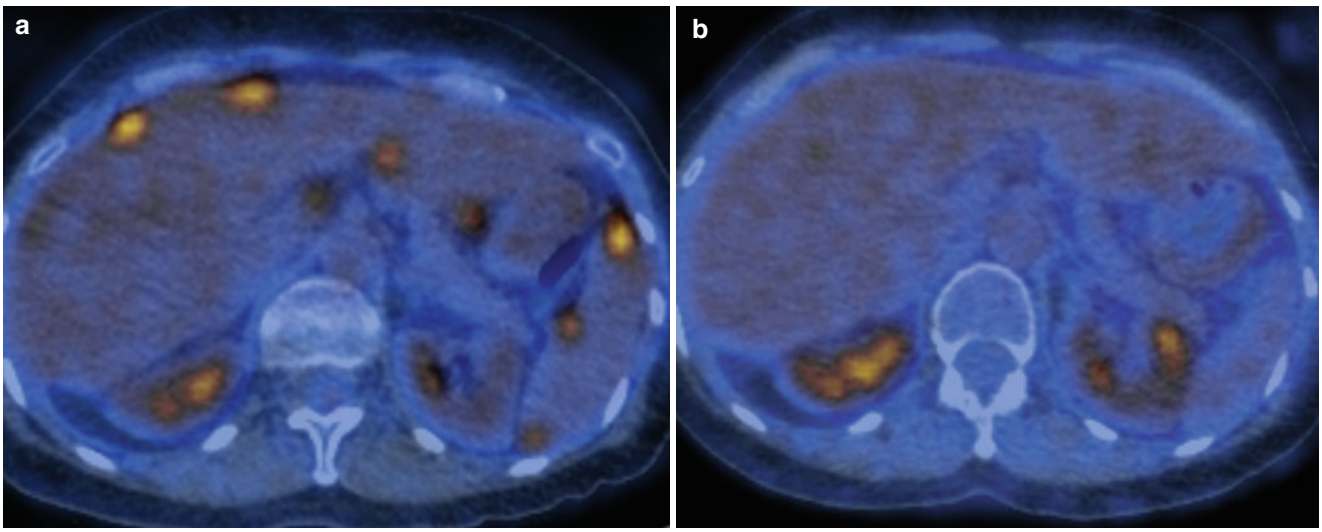

Fig. 21.2 FDG-PET/CT in a woman with recurrent ovarian carcinoma. Several sites of metabolically active disease are demonstrated (**a**). Following a single cycle of chemotherapy, the disease is no longer found to be metabolically active, with only physiological uptake seen in the kidneys (**b**)

for microscopic disease in pathologically positive lymph nodes [73–75].

A prospective, multicenter study in 90 women with suspected recurrence of ovarian cancer showed that ^{18}F-FDG-PET/CT significantly altered the pre-PET management plan in 60 % of cases and that patients with more disease discovered by PET/CT, mainly below the diaphragm, were more likely to progress in the following 12 months [76].

However, in a large prospective randomized study of 1,442 patients, there was no evidence that early detection and treatment of recurrence had any influence on improving patient survival [77]. Thus the role of ^{18}F-FDG-PET/CT in early detection of recurrent disease remains controversial.

Some patients have a CA125 relapse and disease on CT that appears resectable or suitable for localized high-dose radiotherapy. Whether resection or localized radiotherapy improves survival is unknown, but PET/CT may be helpful in identifying other sites of disease questioning the appropriateness of surgery in an individual case and enabling the selection of appropriate cases for localized treatment. As a result ^{18}F-FDG-PET/CT is used at PMCC as a part of staging before salvage surgery. Some authors recommend a prospective study to evaluate the role of ^{18}F-FDG-PET/CT in the stratification of treatment interventions [78]. The DESKTOP I and II studies have identified three factors that predict a high rate of complete cytoreduction in patients with platinum-sensitive disease at first recurrence: (1) complete cytoreduction at primary surgery, (2) good performance status, and (3) absence of ascites [79]. DESKTOP III (NCT01166737) is now under way, evaluating the survival benefit of surgery in these patients. ^{18}F-FDG-PET/CT is not included in the preoperative assessment of patients in this study, although this would be an ideal setting in which to test its role.

Future Prospects

With the evolution of precision medicine, early identification of response to chemotherapy is highly relevant and important. Treating a patient with multiple cycles of ineffective chemotherapy may lead to unnecessary patient morbidity and is not cost effective. In future, it is hoped that early detection of nonresponse to chemotherapy using ^{18}F-FDG-PET/CT could lead to early change in therapy. The emergence of novel targeted radiotracers that reflect the avidity for new molecular targeted chemotherapy agents may increase the precision of treatment choices. Finally, it is possible that detection of sites of disease having the highest FDG avidity in both primary and recurrent disease could direct the best site for biopsy in order to obtain histological information at the most high-grade part of the tumor.

Concluding Comments

- Larger studies are required to ascertain whether the tailoring of radiation treatment fields according to findings on pretreatment ^{18}F-FDG-PET/CT improves survival outcomes in cervix cancer patients. If it is confirmed that this way of individualizing treatment does not translate into improved patient outcomes, then research initiatives must focus on using ^{18}F-FDG-PET/CT as a tool to

triage node-positive patients into a more intensified treatment regimen by either targeted dose augmentation or added systemic therapy.

- More research is required in order to ascertain whether preoperative ^{18}F-FDG-PET/CT can be used to determine which subset of patients can forego lymphadenectomy. Questions remain as to whether an asymptomatic recurrence picked up by surveillance ^{18}F-FDG-PET/CT can lead to increased salvage rates and improvements in survival.
- For ovarian cancer, further research is required to determine ^{18}F-FDG-PET/CT criteria for disease response to chemotherapy with the goal of influencing patient management and preventing futile and costly treatments.

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22 Do Intensity-Modulated Radiation, Image-Guided Radiation, and 3D Brachytherapy Significantly Advance Radiotherapeutic Management of Gynecologic Cancers?

Akila Ninette Viswanathan and Jacob Christian Lindegaard

Summary Points

- 3D imaging has revolutionized gynecologic cancer radiation treatment.
- IMRT and IGRT are available external-beam modalities that may reduce toxicity compared to 3D standard radiation treatment, though cost, time, and long-term effects remain concerns.
- 3D brachytherapy rather than plain X-ray-based planning may improve local control and survival and reduce toxicity.

Introduction

Over the past 10 years, a revolution in the individualization of radiotherapy has occurred. Substantial technological developments in imaging techniques allow for accurate targeting, delivery of high curative doses of radiation, and promise to impart a radiotherapeutic gain for both external-beam radiotherapy (EBRT) and brachytherapy (BT) [1]. With 3D imaging, an increased understanding of tumor and normal-tissue anatomy and the changes that occur during a course of radiation allow individual modification of dose. This improved dose precision may prove successful at reducing local recurrence and toxicities [2–5].

Conventional EBRT, whether using plain X-ray or computed-tomography (CT) simulation, aligns treatment fields with bony landmarks. These field borders were selected to maximize radiation dose coverage of the tumor, at-risk lymph nodes, and adjacent tissues that may harbor residual gross or microscopic disease [6, 7]. For patients receiving post-hysterectomy EBRT, local control rates are excellent [8]. However, acute grade 1 and higher toxicities occur in 30–50 %, and late (>90-day) grades 3–4 complication rates, primarily gastrointestinal (GI) and genitourinary (GU), range from 2 to 5 % [9–11]. For patients with an intact cervix who undergo standard EBRT with BT for cervical cancer, long-term complication rates may be over 10 % [12–14]. The need for more precise tumor targeting in patients with gross disease, and for a reduction in normal-tissue radiation exposure in both patients with intact cervical cancer and those with postoperative microscopic residual disease, has led to the exploration of more conformal radiation treatment options.

CT simulation was widely adopted in radiation oncology clinics in the 1990s. The increasing availability of positron-emission tomography (PET) and magnetic resonance (MR) imaging in these centers increased the fusion of these advanced imaging modalities in the planning of CT-based radiation therapy [15]. In contrast to 3D conformal radiotherapy, in which treatment is delivered by static homogeneous beams and motionless shielding, IMRT may be used to deliver highly conformal and, if desired, complex heterogeneous dose distributions by using miniaturized and motorized shielding leaves that move while irradiating the patient. Arc therapy is a special branch of IMRT in which the complete EBRT fraction is delivered in a continuous rotation of the gantry of the linear accelerator around the patient, with the shielding leaves moving in consort according to a predefined pattern.

Modern linear accelerators incorporate imaging within the treatment room to allow for tracking of the tumor, and this type of advanced gating is a field in rapid evolution. IGRT involves repeated, even daily, localization of the target, to ensure accurate treatment to the tumor while adequately sparing surrounding normal tissues. Both IMRT and IGRT

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allow high doses of radiation to reach discrete volumes by combining imaging information with the actual delivery of radiation.

Similarly, advances in CT- or MR-planned brachytherapy (3DBT) have been shown to reduce normal-tissue toxicities and to potentially improve local recurrence and survival rates. This review will address current controversies in these advanced technologies, that is, IMRT, IGRT, and 3DBT, with an emphasis on the advantages, weaknesses, and potential for future progress with each approach.

Pros and Cons with the Use of Advanced Imaging in Radiotherapy

The advent of 3D imaging and its application to gynecologic malignancies has the advantage of allowing dose escalation to previously incurable regions, thereby improving the therapeutic ratio. Though the use of imaging represents a significant advance, some question the utility. Implementing complex imaging such as MR, CT, or PET scanning is expensive. Requiring multiple scans may have an adverse impact on patients' quality of life. Patients who undergo CT or PET scans receive an additional amount of radiation, though this is negligible compared to the amount of radiation administered for treatment. Contouring on the 3D images is time intensive for the physician and requires training in properly contouring at-risk structures as well as tumor volumes. Planning using 3D imaging also requires familiarity with the region of interest and more physicist time and skill. Given the complexity of the resultant treatment plans, quality-assurance measures need to be robust, comprehensive, and routinely adhered to in a standard fashion. In general, the more complex the treatment plan, the more likely uncertainties will arise in contouring, treatment planning, and, consequently, dose delivery. Whether and how these uncertainties might affect patient outcome is not yet known.

Intensity-Modulated Radiation Therapy (IMRT)

Studies have reported on the feasibility of using IMRT in postoperative cervical, endometrial, and vulvovaginal cancers, as well as in inoperable and recurrent cases. Specific pros and cons related to IMRT are outlined in Table 22.1.

Pro Arguments

IMRT represents one of the most significant advances in radiation dose delivery in the past decade. The ability to conform dose has permitted dose escalation and normal-tissue sparing in ways previously unobtainable.

Table 22.1 Pros and cons of image-based radiation therapy in gynecologic oncology for IMRT, IGRT, and 3DBT

	Pros	Cons
General	Multiple imaging modalities to identify region of interest	Less robust to uncertainties
	Improved therapeutic ratio through highly conformal and heterogeneous dose distributions	More labor intensive
		Quality-assurance measures more complicated
		Economic cost
IMRT	Normal-tissue sparing	Higher integral dose
	Decreased toxicity and morbidity	Increased (albeit small) risk of second malignancies
	Specific dose escalation	Accuracy of contouring and patient setup more critical
	Improved locoregional control	Susceptible to inter- and intra-fraction organ motion
		Tumor regression may require replanning
		Limited evidence for clinical effect in some gynecologic cancers
IGRT	Accounts for organ motion and tumor regression	Poor soft-tissue contrast with kV imaging
	Automated couch repositioning	Registration mainly on bony landmarks
	"Plan of the day" approach	May require fiducial markers
		Increased need for repetitive planning scans
		Learning curve and availability
3DBT	Ensures proper BT applicator placement	Training of BT staff in 3D methods
	Avoids perforation injury	Susceptible to contouring and BT applicator reconstruction inaccuracies
	Individualized BT applicator design and implantation including interstitial component	Requires homogenous dose distribution from EBRT in the region of interest to calculate cumulative dose
	Improved dose coverage of large and/or asymmetric tumors in both space (3D) and time (4D) domains	Depends on radiobiological assumptions for adding EBRT and BT
	Sparing of organs at risk close to BT applicators	

Simulation: Patient Positioning

Several studies have shown that the prone position is associated with a decrease in the small-bowel dose, although others have not shown a clear difference in small-bowel dose or toxicity [16, 17]. However, the prone position is less stable, as patients may move several centimeters while undergoing treatment, due to discomfort. In particular, women with a large panniculus, while most likely to benefit from the prone position, have the most difficulty maintaining a stable position for the duration of an IMRT treatment course. The heterogeneous and highly conformal dose distributions often included in IMRT dose plans are also less robust with regard to the steep gradient in body contour that is produced by immobilization on the bellyboard. Therefore, for IMRT, most institutions implement a supine setup with a custom immobilization device. Though the exposed amount of small bowel may be larger with supine IMRT than with prone 3D in many cases, the comfort of the patient and the ability of the patient to receive IMRT with dose escalation as needed validate this approach for select cases [16].

Contouring: Postoperative Cases

In order to conduct prospective IMRT trials, the Radiation Therapy Oncology Group (RTOG) created a consensus atlas for contouring the postoperative pelvis [18]. Several prospective trials are currently accruing using postoperative IMRT for cervical (RTOG 0742) and endometrial (RTOG 0921) cancer. The recently completed prospective assessment of postoperative IMRT (RTOG 0418) validated the feasibility of IMRT but, when compared to historical controls, did not show a significant reduction in bowel toxicity [19].

Taylor et al. found that, in order to adequately cover the intended nodal regions with IMRT, generally a 7-mm margin, with some modifications such as a 17-mm wide strip along the pelvic side wall joining the external and internal iliac regions and 10-mm extra margin anterolaterally to include the lateral external iliac lymph nodes, encompassed >95 % of the common, external, and internal iliac and the obturator nodes; this 7-mm margin was adopted by the RTOG consensus document [20]. In contrast, based on lymphangiogram data, others recommend 15- to 20-mm margins [21]. However lymphangiography overestimates nodal size and CT is considered more accurate. Special MRI contrast media such as ultrasmall superparamagnetic iron oxide (USPIO), though not routinely available, have provided detailed information on the position of lymph nodes in relation to the major vessels in the pelvis [20, 22] enabling precise target delineation, as these vessels are easily identifiable with contrast on CT. Ahamad et al. [23] found that the volume of normal tissue spared using IMRT was sensitive to small increases in margin size; a 5-mm increase in margin size reduced the volume of spared (>30 Gy) small bowel by 30 %.

Organ Motion in Postoperative Cases

The vaginal vault may move during treatment either due to natural internal (vaginal) movement or due to changes in rectal and bladder filling, as reported by Buchali et al. and others [24–26]. Full- and empty-bladder CT images may be obtained and fused together to contour a vaginal integrated target volume (ITV). The rectum may distend 5–8 cm in some patients due to gas during a course of treatment. Rectal distension may account for significant variation in the rectal and vaginal position, and patients should be asked to empty the rectum prior to simulation and daily treatment.

Contouring: Intact Uterus Cases

Intravenous (IV) contrast for vessel visualization may be used to assist with contouring, though IV contrast can be difficult to time precisely to show uptake in the pelvic vessels at the time of the CT scan. An alternative is MR simulation. The use of MR or PET may be helpful for patients with gross residual disease, involved lymph nodes, or an intact uterus. These images can be fused with the standard CT to assist with treatment planning. Of note, using the PET-derived specific uptake value to define contours of a gross tumor volume is not yet fully standardized as necrotic areas may be missed.

Several studies have assessed inter- and intra-fraction organ motion during a course of EBRT. Given the substantial organ motion in the pelvis, it is not feasible to reliably spare the rectum, given requisite coverage of the uterosacral ligaments in cervical cancer, or the closest regions of the bladder. In order to adequately cover the tumor in cervical cancer, planning margins ranging up to 4 cm must be used to fully encompass the clinical target volume (CTV) for all fractions [27].

Contouring: Vulvovaginal Cancer

The RTOG is currently creating a consensus atlas that will help clarify the necessary margins for both the nodal and primary tumor regions. Beriwal et al. reported their results with IMRT for vulvar cancer and demonstrated a reduction of the V_{30} of small bowel by 27 %, rectum by 41 %, and bladder by 26 % compared to 3D conformal EBRT [28].

Treatment Planning/Dose Distribution

With careful contouring, accurate margin placement for a planning target volume (PTV), and detailed planning, IMRT achieves target coverage similar to that of 4-field (4 F) dosimetry with reduced doses to critical surrounding normal tissues. Roeske et al. [29] found that IMRT reduced the proportion of bladder in the field by 23 %, rectum by 23 %, and small bowel by 50 % compared with 4 F plans. Heron et al. [30] found that IMRT reduced the volume of small bowel receiving >30 Gy by 52 %, bladder by 36 %, and rectum by 66 %. Guo et al. [31] reported that the proportion of organ receiving >45 Gy was 18 % for small bowel, 26 % for rectum, and 43 % for

bladder with IMRT. Georg et al. [32] also found a significant reduction in the amount of bladder, small and large bowel, and rectum irradiated, with a sixfold reduction of dose to the small bowel with IMRT. Tomotherapy, a radiation treatment method whereby radiation is administered slice by slice, reportedly increased the dose to the bowel and pelvic bones [33], whereas arc therapy increased homogeneity and conformity [34]. Arc therapy also shortens beam on time.

Clinical Outcomes

Several retrospective institutional reviews report successful outcomes with IMRT, indicating the potential for significant normal-tissue sparing and reduced toxicity. Roeske et al. [29] found that the volume of bowel receiving ≥45 Gy was the most significant predictor of acute GI toxicity in a cohort of 50 women treated for gynecologic malignancies. Mundt et al. reported highly favorable results in 40 patients treated with IMRT. None experienced grade 3 or higher acute GI toxicity. The use of antidiarrheal medication declined from 75 to 34 % [35].

In a large retrospective series, Kidd et al. reviewed records of 135 women with an intact cervix treated with IMRT for locally advanced cervical cancer and compared them with those of 317 non-IMRT historical controls treated with whole-pelvic RT. They found significantly lower rates of grade 3+ bladder and bowel toxicities among the IMRT cohort (6 % versus 17 %) [36]. There was no difference in post-therapy PET findings 3 months after completing RT, but the IMRT patients had higher rates of cause-specific and overall survival ($p < .0001$). A study by Hasselle et al. [37] reviewed records of 111 cervical cancer patients treated with IMRT, 89 of whom had locally advanced disease with an intact cervix; they reported an overall survival rate of 78 % and a disease-free survival rate of 69, though this was not compared to standard 3D-treated patients. Chen et al. reported outcome data for 109 women; with a median follow-up time of 32.5 months, the 3-year overall survival rate was 78 % and the corresponding disease-free survival rate was 68 % [38]. The rate of acute grade 3+ GI toxicity was low at 2–3 %. Tomotherapy resulted in a grade ≥3 GI toxicity rate of 10 % [39].

IMRT may be of greatest benefit when using an extended field (EF) covering the para-aortic region, which lies in close proximity to the small bowel. IMRT allows dose escalation for patients with para-aortic nodal involvement who may otherwise be deemed incurable. Doses up to 65 Gy are feasible with low toxicity rates if a small bowel dose threshold of V55 < 5cc is implemented [40, 41]. EF-IMRT decreases the dose to the kidneys, spinal cord, bone marrow, and small bowel. Portelance et al. found that the bowel V45 could be reduced more than 2-fold with IMRT compared with 4 F [42]. PET-defined target volumes treated with EF-IMRT allow dose escalation to nodes up to 59.4 Gy for cervical cancer [43, 44]. Salama et al. reported on 13 patients treated with EF-IMRT, 2 of whom had grade 3+ acute and/or late toxicity, indicating the feasibility of EF-IMRT [45]. Gerszten et al. [46] did not report any toxicity with EF-IMRT after short follow-up. For patients with grossly positive residual para-aortic nodes after a hysterectomy for uterine cancer, 3 year rate of nodal control was 86 % and overall survival was 68 % [41]. Small bowel toxicity was minimized when an IMRT constraint of a dose of 55 Gy to less than 5cc of bowel was utilized [40, 41].

Con Arguments

The use of IMRT for gynecologic malignancies remains in some instances controversial, due to concerns about unknown and undetected uncertainties and difficulties of standardization and implementation. IMRT results in a higher integral dose to the surrounding normal tissues, which not only may increase some toxicities if not carefully protected [47] but may also increase the second-malignancy risk [48]. Accurate contouring is critical, as is accounting for both tumor and normal-tissue motion. IMRT requires significantly more time to deliver and experience in the clinic in order to effectively deliver curative treatment.

Simulation: Patient Positioning

Standard radiation techniques for treating locally advanced disease ensure that the entire pelvis, including the vagina, cervix, uterus, ovaries, and bilateral internal and external iliac lymph nodes, receives sufficient radiation dose.

For 3D conformal simulation, patients may be positioned either supine or, order to decrease dose to the small bowel, prone on a bellyboard. Several studies have confirmed the bowel-sparing potential of prone positioning. For 3D conformal treatment set up to bony landmarks, strict patient immobilization is not required, as it is with IMRT. In general, most institutions use CT scanning for simulation.

Contouring: Postoperative Cases

EBRT field borders were historically based on bony landmarks found on X-rays [6, 7]. Since the 1990s, 3D (CT) conformal simulation, also based on bony landmarks, has been standardized and is quick and easy to simulate. A more time-intensive approach is required for IMRT. 3D conformal RT with CT simulation does permit evaluation of the relationship between standard bony-landmark-set field borders and the contoured primary tumor and/or the elective nodal stations, ensuring comprehensive coverage [6]. However, IMRT is much more sensitive to inaccuracies in target delineation. Accurate contouring of the OAR and the CTV is critical. Even the most sophisticated technological equipment for dose delivery will fail if the CTV and the organs at risk are not correctly defined on the imaging study used for radiotherapy planning.

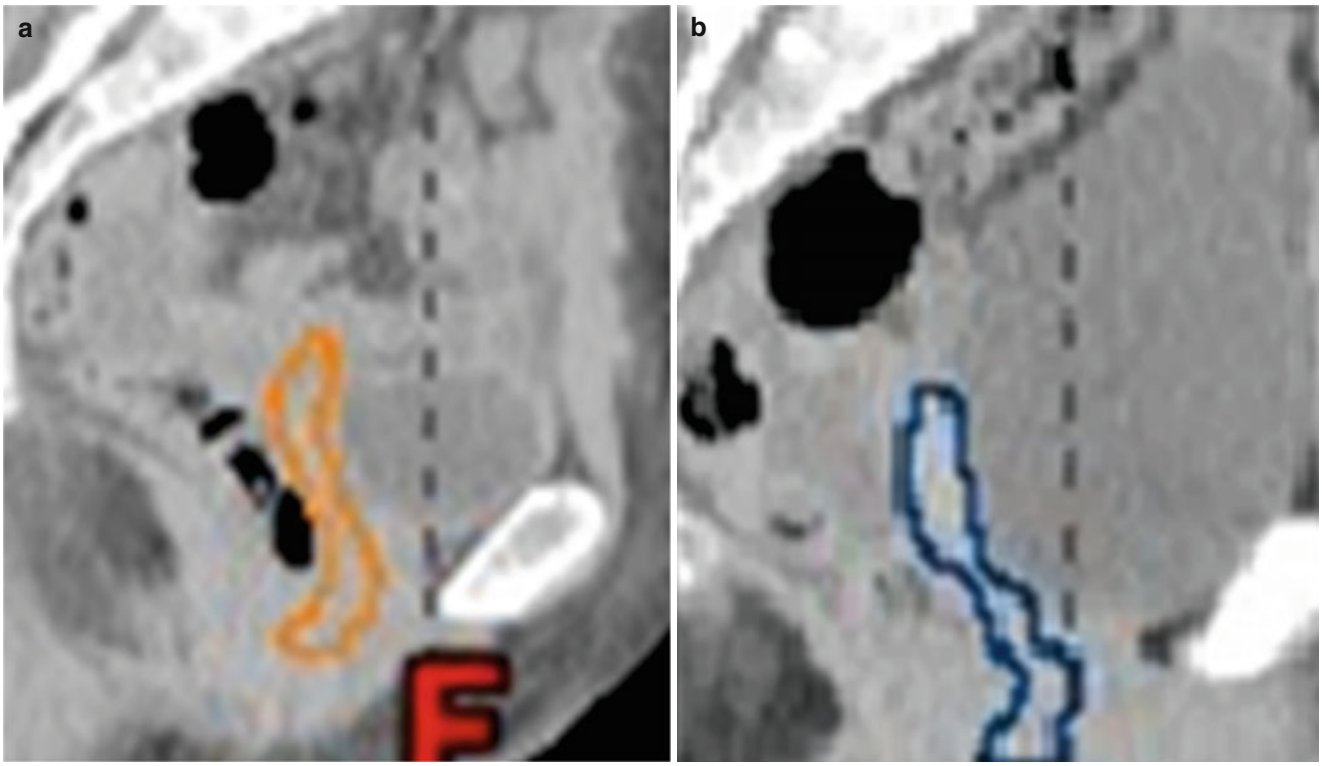

Fig. 22.1 Significant vaginal motion due to empty (**a**) versus full (**b**) bladder can cause the target to move out of the field with an IMRT plan. Therefore, a combined empty and full bladder vaginal volume with large planning margins is recommended

Organ Motion in Postoperative Cases

To correct for vaginal vault motion caused by changes in rectal and bladder filling [24, 25], full- and empty-bladder CT images may be obtained and fused together to contour a vaginal ITV (Fig. 22.1). This requires additional effort on the part of the patient and physician. Bladder emptying and filling are often not reproducible to the same level daily, resulting in errors in estimating movement and the margins calculated for IMRT. There is a potential increased risk of marginal or out-of-field recurrence if the margins are not large enough to account for bladder, rectal, and vaginal movement.

Contouring: Intact Uterus Cases

When compared to 3D conformal treatment, the risk of missing the target is significantly greater in patients with an intact uterus treated with IMRT, and therefore extreme caution is advised when determining the margins required for treatment. For cervical cancer patients with an intact cervix, consensus guidelines for contouring the CTV have been generated, but no acceptable standard has been reached on the margins required for the PTV [49].

Contouring: Vulvovaginal Cancer

Conventional treatment for vulvar cancer ensures relatively uniform coverage of the region of the primary tumor and the regional nodes. Typically, a wider AP field is used, opposed with a narrower PA field that avoids some of the femoral-head region. Fusion of PET/CT scans showing gross disease may be helpful to guide contouring involved regions. The amount of margin required on the primary volume has not been determined in a multi-institutional setting. The primary tumor may extend into the vagina and disease may track laterally from the tumor into the skin-bridge region extending to the femoral/inguinal nodes. In order to avoid a fatal recurrence, comprehensive coverage of this region is recommended [50]. The caveat with standard AP-PA fields is an increased dose to the femoral head, entailing a significant risk of femoral-head avascular necrosis and, in the inguinal region, of wound breakdown, that may cause recurrent skin infections.

Treatment Planning/Dose Distribution

The homogeneity of dose in a 4 field pelvic plan ensures no high- or low-dose regions in the treated area. In contrast, IMRT plans may produce significant overlap regions, with a larger amount of normal tissue receiving a low dose of radiation, and greater heterogeneity in dose in the target region. This has led authors to raise concern that IMRT may be associated with a higher second-malignancy risk than 3D EBRT [48]. IMRT requires significantly more time on the part of

the physician for contouring and the physicist for planning than does standard 3D conformal radiation.

Treatment: Tumor Regression and Organ Motion

The major concerns with IMRT for gynecologic malignancies are intra- and inter-fraction target motion and regression of the tumor in the pelvis. The tumor also does not shrink symmetrically and shrinking in irregular shape may not permit symmetric treatment. Several studies have done interval imaging during a course of radiation and have shown significant inter-fraction motion during EBRT. For patients with cervical cancer with an intact uterus, the uterus may move several centimeters, and bladder-filling changes may affect the cervical and vaginal positions. Therefore, planning margins up to 3–4 cm are required to fully encompass the CTV for all fractions. These large margins result in pelvic fields that closely resemble a 4 F pelvic field.

Clinical Outcomes

To date, no prospective randomized trials comparing IMRT to conformal treatment in gynecological cancers have been completed in the USA or Europe. The likelihood of achieving statistical significance for a primary outcome such as survival is low; therefore proposed randomized trials to date have suggested that toxicity, such as diarrhea rates, may be sufficient. However, patients who receive primary pelvic radiation with a conventional 4 F box technique have low long-term serious (grade 3 or higher) gastrointestinal toxicity rates, and therefore comparison may be difficult. In addition, with acute toxicity reporting, either by the physician or patient, it may be difficult to control for treatment, timing, amount of tissue irradiated, and medical comorbidities.

No phase III clinical evidence exists for the use of IMRT to treat locally advanced cervical cancer. One contouring study did show significant interobserver variability, particularly for the parametrial contours but for the vaginal contours as well [49]. In the regions that have been contoured, IMRT can achieve similar target coverage while reducing normal-tissue dosing.

Image-Guided Radiation Therapy (IGRT)

In order to compensate for the significant organ motion attributable to tumor, bladder, rectum, and bowel movement, IGRT may be indicated. Specific pros and cons related to IGRT are outlined in Table 22.1. For women with postoperative cervical cancer, no trials using IGRT have been reported to date. Pros include the potential to limit radiation to the target and decrease the normal-tissue dose. Difficulties include the time required to reimage, replan, and conduct quality-assurance testing; the cost and training required to perform serial imaging; the burden to the patient of ongoing studies, including the potential need for invasive marker (fiducial) placement; the lack of proven benefit; and the difficulty of reproducible patient setup and stabilization.

Tumor Motion

Similar to IMRT, in order to adequately implement IGRT, target delineation may be improved by using imaging such as PET/CT or MRI. The use of imaging using cone-beam CT (CBCT) for daily treatment verification is necessary (Fig. 22.2). Unfortunately, the images obtained by CBCT often lack sufficient soft-tissue contrast to ensure proper estimations of tumor, bladder, and rectal location. Fiducial markers may be placed, but should be evaluated carefully as they may fall out or shift as the tumor shrinks. Therefore, IGRT requires the implementation of technologies not always available in all centers, such as a CBCT, but also consideration of an MR accelerator, which is in development. Careful planning with regard to the planning target volume (PTV), which accounts for motion above and beyond that accounted for by CBCT, is critical. One review of ten patients who had a CBCT on each day of RT was reported [51]. A rigid registration of the bony anatomy from the planning CT was made. A uniform margin of 15 mm was inadequate and would have failed to cover the CTV in 32 % of fractions and the uterus and cervix in up to 22 % of fractions. Intra-fraction organ motion may be <1 mm, but inter-fraction motion may be up to several centimeters. Daily imaging with replanning treatment approaches may be required to ensure adequate coverage of the CTV.

For women with cervical cancer and an intact cervix, an alternative to daily CBCT is frequent MR scanning, with the advantage of much better visualization of the tumor and normal tissues, throughout the course of EBRT. The required frequency of MRI is not standardized, given the likelihood of both inter- and intra-fraction organ motion and tumor regression. One study assessed MRI scans performed on two consecutive days during EBRT [20]. A total of 33 patients had changes in the position of the uterus and cervix based on registration of three points: the anterior uterine body, the posterior cervix, and the upper vagina. The movement of the cervix was most pronounced in the superior-inferior (SI) and anterior-posterior (AP) directions. The mean difference in AP displacement was 7 mm versus 2.7 mm and for SI was 7.1 mm versus 4.1 mm. SI movement was related to bladder filling, whereas AP movement of the cervix and vagina was affected by rectal filling. In another study of MR during therapy, MR scans were obtained on 20 patients at the start of treatment, then weekly for the first 4 weeks of EBRT. The authors concluded that PTV margins of 24, 27, 23, 26, 11, and 8 mm were needed in the anterior, posterior, right lateral,

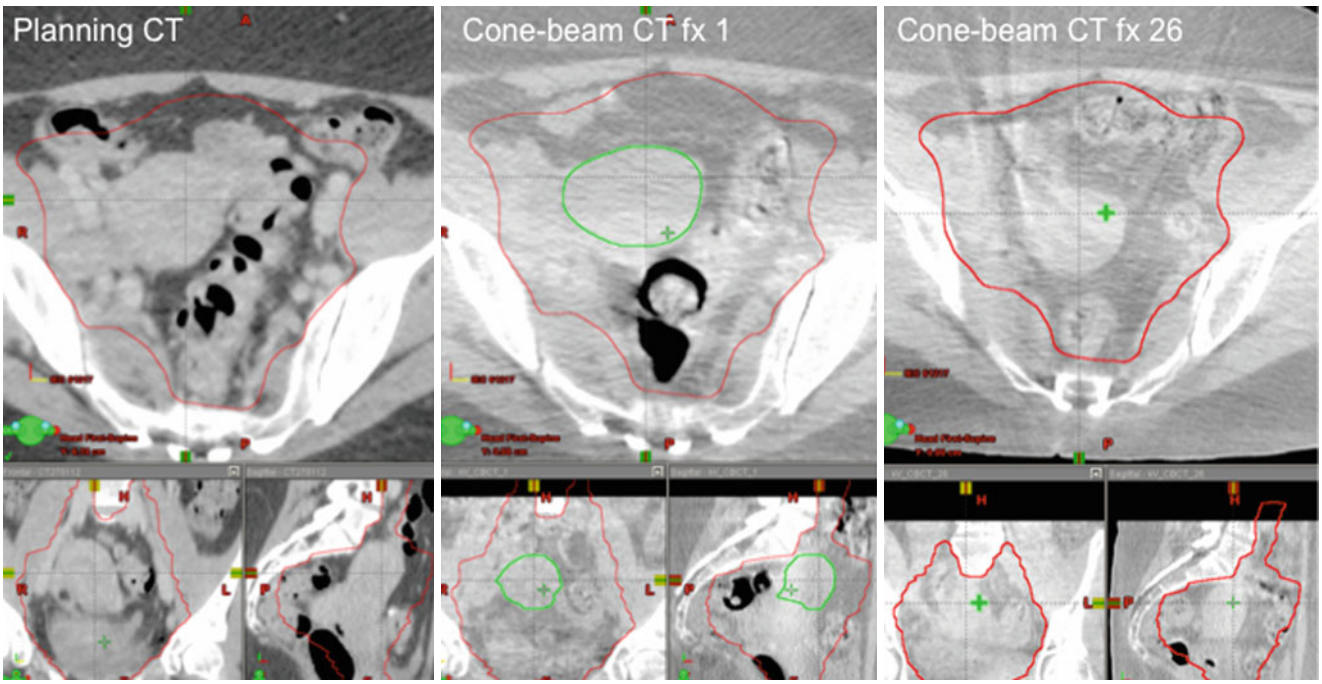

Fig. 22.2 Locally advanced cervical cancer stage IIIB showing the ITV used for planning of whole-pelvic elective IMRT with 50 Gy in 30 fractions (*left panel*). Cone-beam CT performed at fraction 1 (*middle panel*) and at fraction 26 (*right panel*) demonstrates the soft-tissue contrast which can be obtained with this technique to ensure full coverage of, for instance, the uterus (*green contour*) taking into account day-to-day internal movements and tumor regression

left lateral, superior, and inferior directions, respectively, to ensure CTV coverage [52].

Tumor Regression

Tumor regression has been assessed in multiple studies. A review of records for 17 cervical cancer patients showed 50 % tumor regression 21 days after 30.8 Gy [53]. Another study of 16 patients showed a 62 % mean volume reduction after 45 Gy [4]. Fourteen patients who had an MR scan pre-treatment and once during treatment showed a 46 % (range 6–100 %) decrease in primary gross tumor after 30 Gy [54]. A review of records for 80 cervical cancer patients who underwent four MR scans (at diagnosis, 2–3 weeks into RT, immediately after RT, and 1–2 months after RT) found that both tumor volume and regression ratio were strongly correlated with local recurrence. The strongest predictor of local recurrence was the pre-RT volume and the regression ratio at 4–5 weeks during RT [55].

Organ Motion

Similar to what was described with IMRT, organ motion remains an issue that is difficult to discern during treatment, given poorly defined normal-tissue structure. To characterize organ motion, records of 20 patients were analyzed at Princess Margaret Hospital, and the vector motion of bladder, rectosigmoid, and uterus ranged up to 3.2, 4.0, and 4.5 cm, respectively, mainly in the AP and SI directions. All patients had a standard bowel and bladder preparation schedule; nevertheless, the range of bladder filling was 9–693 cc, and rectosigmoid volume was 25–276 cc [56]. Several studies have looked at the relationship between rectal and bladder filling and uterine and cervix movement. Buchali et al. [26] showed that displacement superiorly was the most common form of movement. Tyagi et al. [51] demonstrated superior displacement of the CTV with bladder and rectal filling and posterior displacement with rectal filling alone.

Tumor regression and internal motion of the uterus, bladder, rectum, bowel, and even the vagina can be quite large during EBRT [4]. Given the time and resources required, IGRT has not been implemented in most clinics in the USA and continues to be studied in select institutions. Importantly, the dosimetric impact of organ and tumor changes may, in theory, be less than expected, especially if an appropriate strategy is used that combines IGRT with adaptive replanning. Stewart et al. showed in a study of 33 cervical cancer patients that even a 3-mm PTV margin ensured acceptable CTV coverage in 73 % but therefore missed 27 % of cases and that this could be improved with weekly replanning [57]. The same group has shown that a 5-mm PTV margin ensures adequate CTV coverage with daily image-guided setup [58]. Given the

concerns about organ motion, which are not an issue with the large fields routinely used with 3D conformal radiation, 3D may be used as the standard treatment. The use of IGRT, which requires extensive treatment planning, remains an area of active investigation by several clinics worldwide.

3D Brachytherapy

Introduction

Definitive radiotherapy in gynecologic malignancies requires a combination of regional EBRT combined with a boost of BT to the primary tumor in order to ensure both local and regional tumor control [59]. Local control is poor for patients who cannot receive BT to the primary tumor for various reasons [60], while EBRT is needed to obtain pelvic nodal control [61]. The whole pelvis and sometimes also the para-aortic nodes are treated with EBRT to approximately 45–48 Gy using 1.8 Gy/fraction. Following this, BT with a tandem inserted into the uterus (tandem and ovoids or tandem and ring applicators) [13] is used to bring the primary tumor to doses in the range of 80–90 Gy, depending on tumor size, historically with the dose recorded at point A [62]. Recent surveys in the USA and Europe demonstrate the increasing use of 3DBT, with dose given to the at-risk volume rather than to a prespecified point [63, 64].

Pro Arguments

Feasibility

Proper applicator placement, as assessed with plain X-ray-based imaging after insertion, with the ovoids symmetric, the vaginal packing not displaced, and the tandem properly inserted, significantly improves local control and disease-free survival [65]. Using ultrasound to assist with insertion may facilitate proper tandem placement [66]. CT or MR imaging used in treatment planning may also be linked to a significant survival benefit when compared to plain X-ray dosimetry [67]. A report from 1992 using MR to assist with treatment planning for cervical-cancer brachytherapy demonstrated the feasibility of MR scanning after insertion to visualize the tumor volume [68]. A study from the Medical University of Vienna using CT-based planning showed highly favorable results [69], as did those from the USA [70, 71]. Over the past decade, research using either real-time MR guidance [72, 73] or post-insertion MR-based planning to assist with tumor delineation has blossomed. Evaluations of the dosimetric consequences of MR-based planning [74] have shown favorable results compared to traditional point A plans [75–77]. A direct comparison of CT to MR planning after insertion in the same patient showed that the CT-contoured images were wider in the region of the parametria; this may be of benefit as MR may show these regions as grey areas, and physicians learning MR-based contouring may miss these critical regions [78]. No differences in other parameters were seen [79]. Contouring guidelines have been published that aid the physician in contouring on MR in a standardized fashion [80, 81] and contouring guidelines for CT have been established [78].

Clinical Outcomes

The first prospective study using mainly CT-based planning in comparison to plain X-ray-based planning, the French STIC trial, showed significant improvements with CT in the subgroup receiving chemoradiation for locally advanced disease in toxicity reduction (22–2.6 %), improvement in local control (74–79 %), disease-specific survival (55–60 %), and overall survival (65–74 %) [81]. Retrospective clinical outcome reviews with 0.2 T MR from the Medical University of Vienna, from Institut Gustave Roussy, and from Aarhus similarly show improvements [67, 77, 82, 83]. A comparison of outcome in sequential cohorts of patients from Vienna showed improvement as higher doses were realized in the tumor target with no apparent influence on the rate of severe morbidity [62]. Other institutional series with CT [84, 85] confirm that very high rates of local control (90 % and above) are achievable at the cost of very limited rates of severe morbidity. One recent report using 3 T MR for both intracavitary and interstitial gynecologic brachytherapy shows the feasibility of high-strength 3 T MR units for gynecologic brachytherapy [87].

Con Arguments

Feasibility

As with IMRT and IGRT, 3DBT requires resources, including appropriate image-safe applicators and equipment; imaging capability, either in radiology or radiation oncology; and time to contour and plan appropriately. Though resources may hinder the implementation of 3DBT, studies using ultrasound demonstrate feasibility [88], and those with CT show feasibility and excellent outcomes [81, 86].

Conclusions

With advances in imaging technology, we now have the capability to target radiation dose much more precisely than was feasible over the past 100 years. The individualized approach to radiation improves the therapeutic ratio. In treating regions such as the para-aortic nodes, where positive nodes previously rendered patients incurable but for which they now may receive definitive radiation, a clear benefit to the use of high-technology treatments such as IMRT can be demonstrated. Use of IMRT in the postoperative setting has been shown to result in lower rates of

gastrointestinal toxicity. In other areas, such as standard treatment for locally advanced cervical cancer, the benefits of IMRT and IGRT have yet to be determined, and the investment of time and resources may not be justified. Initial results have shown that 3DBT improves survival and decreases toxicity and should be moved forward as a standard approach given the potential benefits to patients.

Future Directions

Further research is needed to ascertain the best role and indications for functional imaging. Though we know that inter- and intra-fraction organ motion occurs, the best way to manage these changes has not been resolved. Solutions may include advances in onboard imaging with MRI, miniaturized in vivo dosimetry for BT, deformable registration with voxel-by-voxel dose determination, and advances in treatment planning system image-fusion capabilities. Large multicenter studies, especially randomized trials evaluating IMRT, IGRT, and 3DBT, are needed to determine the requisite dose-volume parameters and confirm the improvements in clinical outcomes, including morbidity and quality of life, that they may impart.

Concluding Comments

- In the future, how best to create an individualized approach to radiation using 3D imaging will be further explored.
- Use of IMRT in the postoperative setting has been shown to result in lower rates of gastrointestinal toxicity. Whether this holds true for intact cervical cancer and other gynecologic cancer sites must be studied further. The benefits of IMRT and IGRT have yet to be determined, and the investment of time and resources may not be justified.
- Initial results have shown that 3DBT improves survival and decreases toxicity and should be moved forward as a standard approach given the potential benefits to patients.

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What Is the Place of Hormone Replacement Therapy in Ovarian, Endometrial, and Breast Cancer?

23

Inge T.A. Peters, Fiona C. Brownfoot, J. Baptist Trimbos, and Martha Hickey

Summary Points

- HRT and risk of gynecological and breast cancer:
  - Level one data have shown combined HRT appears to increase the risk of breast cancer, at least with >5 years of use. It is uncertain whether estrogen alone increases breast cancer risk. Women who have used estrogen alone HRT and then discontinued use appear to have a reduced risk of breast cancer, but the mechanism of this reduction is not clear.
  - Observational data suggest that cyclic HRT may slightly increase the risk of ovarian cancer, while continuous HRT use does not lead to this increased risk.
  - Unopposed estrogens increase the risk of endometrial cancer, while combined continuous HRT leads to a reduction in the incidence of endometrial cancer.
  - Short-term HRT post-prophylactic oophorectomy in BRCA-positive patients has not been shown to increase the risk of breast cancer and can be considered for treatment of menopausal symptoms and preservation of bone density in this group.
- HRT and risks of cancer in patients with previous gynecological or breast cancers:
  - Estrogen alone HRT appears to be safe following endometrial cancer.
  - Estrogen alone HRT following epithelial ovarian cancer appears to be safe. Estrogen is avoided after granulosa cell tumors although there is little evidence to support this.
  - HRT and tibolone both have been shown to increase the risk of new breast cancers or recurrence in patients with a personal history of breast cancer and should be avoided. The safety of vaginal estrogens after breast cancer is not proven. In cases of symptomatic need, estriol cream is preferred over local estradiol.

Introduction

The menopause is the final menstrual period. The term perimenopause refers to the time from the onset of symptoms (usually vasomotor symptoms or menstrual cycle changes) until 1 year after the final menstrual period and is a more clinically useful concept [1]. The perimenopause usually begins at around 47 years and the menopause at around 51 years. Women are considered postmenopausal when menstruation has ceased for 12 months. At this time, blood serum levels of follicle stimulating hormone (FSH) commonly rise to a value of about 50 IU/L and endogenous estradiol levels are usually <100 pmol/L. Endocrine changes at menopause may have a number of symptomatic and health effects. Common symptoms include hot flushes and night sweats (vasomotor symptoms), vaginal dryness, sleep disturbance, and mood disturbances [2]. Bone density usually declines following menopause, and there is an increased longer-term risk of fracture. Hormone replacement therapy (HRT) as estrogen or estrogen plus progestagen effectively

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alleviates these climacteric symptoms and reduces fracture risk during the duration of use. However, HRT might also be associated with adverse consequences. This chapter provides an overview of the relationship between HRT and gynecological cancers and the role of HRT for the treatment of menopausal symptoms in women with a history of gynecological cancer.

HRT and Ovarian Cancer Risk

Ovarian cancer affects more than 20,000 women annually and is the fifth most common cause of cancer mortality in the USA [3]. Women diagnosed with ovarian cancer have an estimated 5-year survival rate of 80 % for stage I disease and 10–20 % for stage IV disease [4].

The exact etiologic factors are still poorly understood, but the development of ovarian cancer is thought to be related to repetitive ovulatory activity since women with any pregnancy or oral contraceptive use have a lower risk of getting the disease. Moreover, a strong association with genetic mutations is found, and up to 10 % of ovarian cancers are due to an inherited predisposition, including hereditary breast and ovarian cancer (BRCA1 and 2 gene mutations) and hereditary non-polyposis colorectal cancer (Lynch II) syndromes [5].

Several other hypotheses to explain the etiology of ovarian cancer have been formulated. The gonadotropin hypothesis states that high gonadotropin levels induce proliferation of ovarian epithelium and therefore increase the risk of ovarian epithelial cancer. Another hypothesis suggests that carcinogens might be transported retrogradely through the fallopian tubes [6].

The subtitle of this paragraph leads one to suspect that hormone replacement therapy also influences the risk of ovarian cancer. The Million Women Study, a large cohort study conducted in the UK, showed that women who currently use HRT have 1.2 times more risk of developing a fatal ovarian malignancy compared to those who have never taken HRT. This incidence increased significantly with the duration of HRT use. Interestingly, past users, who were defined as women who stopped taking HRT before the diagnosis of ovarian cancer, were not at higher risk. The reasons for this observation are not known [7]. A case–control study from the University of Queensland, Australia, revealed similar results. Ovarian cancer risk was inversely related to the time since the last use of estrogen regimens. Compared with never users of HRT, current users were at highest risk (OR 3.92; 95 % CI 1.32–11.6), women who had ceased use within the last 5 years were at intermediate risk (OR 2.09, 95 % CI 0.90–4.89), and women who had last used estrogen replacement therapy more than 5 years ago were at lowest risk (OR 1.45; 95 % CI 0.90–2.32) [8].

In the Million Women Study, no differences were seen between the various types of constituents or administration methods [7]. By contrast, a Swedish nationwide case–control study demonstrated an elevated risk in ever users of estrogen replacement therapy combined with sequentially added progestins, but no increased risk for continuous combined estrogen replacement therapy [6]. This concurs with the results obtained by Lacey and colleagues. These authors stated that the risk of ovarian cancer was noticeably higher in women taking sequential (RR 1.94, $P=0.01$) than continuous (RR 1.41, $P=0.14$) regimens in comparison to women who never used HRT [9]. Such findings might be consistent with the aforementioned retrograde hypothesis. Since HRT with sequentially added progestins is associated with regular withdrawal bleeding, one might suggest that in women receiving these treatments more carcinogens could be transmitted through the fallopian tubes. Similarly, women with a prior hysterectomy or tubal ligation are less likely to develop ovarian cancer than patients having an intact reproductive system [6, 8]. Nonetheless, Rodriquez and co-workers postulated a direct effect of postmenopausal use of estrogens on ovarian cells by promoting proliferation and malignant cell transformation [10].

Some studies have evaluated the relative risk of various histological types of ovarian cancer in patients using HRT. Beral et al. noted a higher incidence of serous ovarian carcinoma among women receiving HRT compared to never users [7]. Purdie et al. found a higher use of estrogens among cases with endometrioid and clear cell cancers ($P=0.06$) and argued that endometrioid and clear cell tumors are generally considered as the counterpart of the same carcinomas of the endometrium, showing both proliferative and secretory modifications [8]. Despite limited power, Danforth et al. also found a slightly stronger association for endometrioid carcinomas [11]. Hence, a correlation with endometrial cancer might be drawn in which the relationship with estrogens is similar to endometrioid endometrial carcinomas. Whether HRT use is actually linked to tumor histology still remains unclear.

In conclusion, current use of sequentially administered hormone regimens seems to result in a higher risk of developing ovarian cancer, whereas past users have the same risk as never users. The use of continuous combined HRT has not been associated with an increased ovarian cancer risk. The relationship between HRT and ovarian cancer development remains poorly understood.

HRT and Endometrial Cancer Risk

Endometrial cancer affects 40,000 American women per year and is known as the most common malignancy of the female genital tract in the developed world [5]. The 5-year

survival rate is 85–90 % for women having stage I disease. The estimated survival rate for patients with advanced disease is much worse, about 20–25 % [12].

Exposure to a continuous hyperestrogenic state is the main predisposing condition for developing endometrial cancer as estrogens potentiate glandular and stromal proliferation. This exposure can be from endogenous as well as from exogenous sources. Endogenous sources include nulliparity, late menopause, polycystic ovary syndrome, chronic anovulatory cycles, diabetes mellitus, obesity, and estrogen-secreting tumors of the ovary. Tamoxifen use and unopposed estrogen as HRT are among exogenous factors [5].

It is common knowledge that progestagens counteract the estrogenic effect on the endometrium. The Million Women Study was conducted to learn more about the relation between the use of different types of HRT and the incidence of endometrial cancer and showed that the risk of endometrial cancer tended to be lower in women who reported using continuous combined HRT, defined as progestagens added to estrogens on a daily basis (RR 0.71; 95 % CI 0.56–0.90; $P=0.005$) [13]. This effect of continuous suppletion of progestagens was confirmed by a study performed at the Helsinki University, Finland. The use of estradiol plus a levonorgestrel-releasing intrauterine device system resulted in a decreased risk of endometrial cancer (OR 0.39; 95 % CI 0.17–0.88) [14]. The findings were also in accordance with the results reported by Wells et al. These authors took endometrial aspiration biopsies before and after administration of continuous combined hormone replacement therapy and reported that long-term treatment of daily 2 mg estradiol and 1 mg norethisterone acetate for up to 5 years did not increase the risk of endometrial hyperplasia nor malignancy. Continuous combined HRT appears to reduce the risk of endometrial cancer [15].

Regarding the protective effects of sequential progestagen use, there is considerably less evidence in the literature. In the majority of studies, sequential hormone regimens were defined as progestagens added to estrogen therapy during 10–14 days once a month. Use of sequential estradiol-progestagen therapy appeared to be associated with a diminished risk for endometrial cancer, as long as the estimated exposure time remained less than 5 years. Contrarily, sequential progestagen use for more than 10 years resulted in a remarkably elevated endometrial cancer risk of 38 % (95 % CI 1.15–1.66) [14]. Beral and colleagues have shown that the relationship between HRT and endometrial cancer is mainly determined by body mass index. They reported a reduced prevalence among obese users of cyclic combined HRT but demonstrated a higher incidence in women who were not overweight [13]. According to Razavi and co-workers, short-term sequential use was associated with an increased risk, irrespective of the patient's body mass index [16].

Several plausible explanations about obesity, hormone replacement therapy, and endometrial cancer risk have been put forward. The enzyme aromatase, which is mainly expressed in adipose tissue, catalyzes the conversion of steroids to estrogens and primarily accounts for the extraglandular estrogen formation. Therefore, a higher level of circulating endogenous estrogens can be found in obese women. As mentioned above, the risk of endometrial cancer increases with elevated amounts of circulating estradiol from external sources. Nonetheless, this risk seems to be restricted to non-obese women. In overweight women, suppletion of exogenous estrogens has only a small additional effect [17].

In summary, estrogen-only therapy increases the endometrial cancer risk, but continuous combined HRT reduces endometrial cancer risk. The impact of sequential HRT on endometrial cancer risk is controversial, and the impact may depend on BMI (body mass index) as well as the nature, duration, and dosage of progestagens. Further research is needed to draw more reliable conclusions.

HRT and Breast Cancer Risk

Breast cancer is the most common cancer in women and will affect 1 in 8 over the course of their lifetime. Due to multiple causes, among which the introduction of mass population screening, breast cancer incidence has increased markedly and is still rising [18, 19]. It is the leading cause of death in women aged 40–55 years of age [19]. Mortality from breast cancer is fortunately on the decrease, likely a result of early detection and improved therapy [20].

Prolonged exposure to endogenous ovarian hormones is a risk factor for breast cancer [21]. This is supported by an increased risk with early age of menarche, late age at menopause, nulliparity [22–24], late age at first birth [25], and older age [18]. Postmenopausal women who are obese have higher circulating levels of estrogens [26] and are at increased risk for breast cancer and mortality from the disease [27, 28].

Estrogen and Progesterone HRT and Breast Cancer Risk

Ovarian sex steroids are thought to contribute to breast cancer risk. The association between estrogen and breast cancer is supported by numerous epidemiological and experimental studies. Breast cancer is 100 times more common in women than in men [18]. Men who are exposed to estrogen therapy have an increased incidence of breast cancer [29]. Estrogen stimulates breast cancer cells in vitro [30], and breast cancer is significantly decreased in women undergoing oophorectomy before age 50 years [31]. Together, these data strongly suggest that estrogen contributes to oncogenesis in breast

cancer. Progesterone perhaps plays a larger role in development of breast cancer than was first appreciated [18]. In vivo studies have shown that progesterone stimulates breast cell proliferation at physiological levels [32]. Cellular proliferation is the underlying process leading to DNA damage accumulation and development of cancer [18]. Perhaps it is the progesterone component of early menarche and earlier development of regular ovulatory cycles and rapid regular menses that increases this risk rather than the estrogen component [33, 34].

There have been numerous prospective and retrospective trials of hormone replacement therapy and its role in breast cancer risk, with the majority concluding that combined estrogen/progesterone HRT increases the risk of breast cancer. The Million Women Study included 1,084,110 women aged 50–64 years and recruited women when attending for their mammogram. Current users of HRT were more likely than nonusers to develop breast cancer (RR 1.66; 95 % CI 1.58–1.75) and were more likely to die from their disease (RR 1.22; 95 % CI 1–1.48) [35]. Similarly, the Women's Health Initiative (WHI), the only randomized control trial including women aged 50–79 in the USA performed primarily to determine effects of HRT on cardiovascular health, noted a nonsignificant trend to increasing breast cancer risk that caused the cessation of the trial (RR 1.26; 95 % CI 1.00–1.59) [36].

The incidence of breast cancer increased significantly with increased duration of use [37]. Pooled epidemiological data show a 15 % increase in breast cancer incidence if HRT is used for less than 5 years and a 53 % increase if it is used for more than 5 years. This is consistent with the WHI trial, which showed a 26 % increase in breast cancer risk if HRT was used for more than 5 years. In the WHI, the harm ratio was only increased in women with prior hormone use and was not higher in women with a family history or other estrogen related risk factors [36], further implicating HRT as causative. There was no increased risk in past users [18]. While the WHI was not powered to assess mortality, observational studies show conflicting results. A meta-analysis by Nanda et al. [38] concluded that the risk of death from breast cancer was reduced in those taking HRT; however, the Million Women Study showed a borderline increase in mortality [28]. The Million Women Study demonstrated that the rate of breast cancer was increased regardless of estrogen or progesterone dose, sequential or continuous regimens, or route including oral, transdermal, or implanted estrogen preparations [35].

There is significant discrepancy with regard to the prognostic features of tumors seen in HRT users. In observational studies, HRT-associated breast cancer was found to be associated with smaller tumor size at diagnosis [39–41]. Many have also shown a reduction in lymph node spread [41]. Stage 1 disease was more common [41–43]. Receptor-positive tumors are a more contentious issue with observational studies being divided, some showing that they occur more commonly in HRT users [41, 44, 45] and others showing that they occur less commonly [43, 46]. Many observational studies have found an increase in tumors with favorable histologies (in situ, tubular, medullary, papillary, and mucinous) [42, 47, 48]. They tend to be well differentiated [49]. No increase in expression of protein Neu, Bcl-2 gene, protein p53, and E-cadherin could be seen in the majority of trials [50, 51]. In contrast, the much larger placebo randomized controlled WHI trial showed that tumors were found to be significantly larger among HRT users when compared to placebo users (mean +/– SD: 1.7 cm +/– 1.1 vs. 1.5 cm +/– 0.9; $P=0.04$) [49]. There was an increase in nodal disease (25.9 % vs. 15.8 % $P=0.03$), and the tumor stage was more advanced in HRT users (metastatic: 25.4 % vs. 16 %, $P=0.04$). There was no difference in histology, grade, estrogen, or progesterone receptors between the HRT and placebo groups [49]. This discrepancy could be due to the inherent risk of bias associated with selection and collection of data in retrospective analysis, confounding factors not accounted for in these studies, publication bias, and increased screening in the HRT user group leading to early detection of disease. In regard to the WHI, only one regimen was investigated and an older cohort was studied.

Estrogen Only and Breast Cancer Risk

The impact of estrogen-only HRT on breast cancer risk differs from that of estrogen and progestin in combination. HRT was first released in the 1960s in the form of estrogen-only preparations and grew in popularity up to 1974, when 28 million prescriptions were filled [52]. In 1975 a link between unopposed estrogen preparations and endometrial cancer [53, 54] was recognized and a decline in usage followed, until progestins were added and were found not only to reduce the increased risk but to be protective for endometrial cancer [55]. It was incorrectly assumed that the protective effects of progestin effect would extend to breast cancer [56].

There have been numerous observational studies with varying findings regarding risk of breast cancer with estrogen-only HRT [57]. The Million Women Study demonstrated an increased risk (RR 1.30; 95 % CI 1.21–1.40; $P=0.0001$) after 1–4 years of use that increased with continued use. This was less than the risk for combined estrogen and progesterone preparations [35]. In contrast, the Nurses' Health Study – a prospective cohort study primarily surveying the effect of HRT on cardiovascular health – initially showed a nonsignificant reduction in breast cancer risk [58]. Only after 20 years of estrogen-only use did women experience an increase in breast cancer risk (RR 1.42; 95 % CI 1.13–1.77). The risk in both of these studies was not dose dependent, which is consistent with other studies although very few women were prescribed doses higher than 0.625 mg

of equine estrogen. It is not known whether breast cancer risk with estrogen-only HRT is dose dependent. In the Nurses' Health Study, breast cancer risk was increased in those with a BMI <25, and the tumor type that predominated was ER+/PR+ breast cancer [58].

The estrogen-only arm of the WHI was continued for 7.1 years and was terminated 12 months early due to an increased risk of stroke and little benefit in cardiovascular health [59, 60]. The initial analysis found a nonsignificant reduction in the risk of breast cancer (RR 0.77; 95 % CI 0.59–1.01) [60]. Recently, an analysis 10.7 years post-initial recruitment has been conducted to assess outcomes. Overall there was a significant reduction of breast cancer in the estrogen-only HRT group (RR 0.77; 95 % CI 0.62–0.95) compared to the placebo group. The reduction in breast cancer risk was consistent across all age groups studied. Postmenopausal women aged 50–59 years randomized to estrogen only had a lower risk of death (0.73 (0.53–1.00)) and those in their 60s had no increased risk (RR 1.04; 95 % CI 0.88–1.24) [60].

There is increasing awareness that it is the progesterone component that is carcinogenic [61]. As described previously, maximum mitotic activity occurs in the breast in the luteal phase of the menstrual cycle [62]. There is a known association between increased mammographic density and development of breast cancer [63] with a greater increase in mammographic density for women treated with combined HRT compared to those treated with estrogen-only HRT [64]. Perhaps confounding factors reduced this risk of breast cancer in estrogen-only users. For instance, oophorectomy is protective against breast cancer, and more women undergoing hysterectomy will have estrogen-only HRT following a concomitant oophorectomy [57]. Many observational studies do not detail the proportion of patients that have had oophorectomy. Furthermore, other confounders including age, race, BMI, and premenopausal or perimenopausal and socioeconomic status may not have been accounted for in these observational studies [57]. While the WHI supplies best evidence, there are limitations to this also [59]. Only one dose of oral estrogen was trialed and long-term use greater than 7 years cannot be assessed. High rates of discontinuation or cross perhaps could have lead to dilution of the effect of estrogen-only medication [59, 60].

Estrogen-only HRT appears to have a protective effect on risk of breast cancer when taken for a period of less than 7 years [59, 60]. Caution must be exercised with prolonged use due to the potential increase in breast cancer after 20 years of use [58].

HRT and BRCA Mutation Carriers

BRCA1 and BRCA2 are the two major susceptibility genes involved in hereditary breast and ovarian cancer. Women who carry a BRCA1 and BRCA2 mutation have a 54–85 and 45 % lifetime risk of developing breast cancer, respectively, and a 18–60 % and 11–27 % lifetime risk of developing ovarian cancer, respectively [65]. In these women prophylactic salpingo-oophorectomy is recommended at age 35 or after childbearing is complete to lower the risk of breast, ovarian, and fallopian tube cancer [66]. However, due to the loss of ovarian function, this treatment might be associated with menopausal symptoms and sexual dysfunction. To mitigate these symptoms, hormone replacement therapy can be considered.

Finch et al. conducted a study to evaluate the extent to which salpingo-oophorectomy influences quality of life. Women who were premenopausal at the time of surgery experienced post-surgery worsening of vasomotor symptoms, i.e., hot flushes and night sweats, and a decline in sexual functioning ($P<0.0001$). Women who received additionally HRT, however, had significantly fewer symptoms ($P=0.0003$) and reported better sexual functioning ($P=0.015$) than women who did not receive HRT, although baseline measures of sexual function were not made [67, 68]. The results were in line with those demonstrated by Madalinska and co-workers. These authors performed a nationwide cross-sectional observational study and showed that women using HRT after prophylactic oophorectomy were less likely to experience vasomotor symptoms than nonusers ($P<0.05$). Nonetheless, compared with premenopausal women, HRT users reported these symptoms more frequently. Sexual discomfort in terms of vaginal dryness and dyspareunia was also more often observed ($P<0.01$) [69].

The safety of HRT in women at increased inherited risk of breast and ovarian cancer is not resolved. HRT did not appear to adversely influence the risk of ovarian cancer [70] in a matched case–control study in 162 matched sets of women carrying a mutation in either the BRCA1 or BRCA2 gene. The PROSE study showed that HRT did not alter the protective effect of prophylactic oophorectomy (HR 0.37; 95 % CI 0.14–0.96), neither did progesterone only nor combined therapy. However, substantial differences were observed between the cases and control group [71]. According to Armstrong et al., the decision to take HRT after oophorectomy should be predominantly based on quality of life issues rather than life expectancy, as prophylactic oophorectomy lengthened the life expectancy irrespective of the use of HRT. In subjects who underwent bilateral oophorectomy, small changes in life expectancy were seen when surgical therapy was followed by HRT until the age of 50, the expected time of natural menopause. The safety of long-term HRT use in women at increased inherited risk of breast and/or ovarian cancer is not known. For high-risk women who undergo both risk reducing bilateral salpingo-oophorectomy and prophylactic mastectomy, both ovarian and breast cancer risks are reduced, and this may modify decision making around HRT use [72].

In conclusion, hormone replacement therapy seems to have a positive effect on quality of life after prophylactic oophorectomy, although presurgical levels of well-being cannot be achieved. HRT does not appear to influence the protective effect of prophylactic oophorectomy and might therefore be considered in BRCA mutation carriers who do not have a personal history of breast cancer.

HRT After Endometrial and Ovarian Cancer

Iatrogenic menopause following cancer treatment can have drastic adverse effects on quality of life. Due to the sudden onset, younger age, and the effect on common physical and psychological problems of cancer therapy, these symptoms may be more intense than those of natural menopause. In healthy women, hormone replacement therapy is usually the best treatment option to relieve these symptoms and maintain quality of life. Limited data, however, address the safety of HRT in women with a history of ovarian or endometrial cancer.

Several studies were performed to investigate the survival in patients who were diagnosed with endometrial cancer and subsequently treated with hormone replacement therapy. The results seem to be favorable: none of the studies showed an increased incidence of recurrent disease. A prospective case–control study by Ayhan et al. found no significant difference with respect to prognosticators between HRT users and the control group, indicating that immediate postoperative use of continuous combined HRT was not associated with a higher recurrence rate in endometrial cancer survivors [73]. Suriano et al. compared 75 patients diagnosed with FIGO stage I–III endometrial cancer with a matched control group. The patients in the HRT group used 0.625 mg oral conjugated equine estrogens, and nearly half of them received 2.5 mg medroxyprogesterone acetate in addition to estrogen on a daily basis. Their analysis revealed a lower recurrence rate and a significant longer disease-free interval in the HRT group ($P = 0.006$) [74]. These results are promising, though it should be mentioned that only small sample sizes were used. Moreover, the authors did not distinguish between patients who were treated with estrogen-only therapy and those who used continuous combined HRT. The Gynecologic Oncology Group (GOG) conducted a randomized double-blind trial and reported similar outcomes: 2.3 % of 618 HRT patients and 1.9 % of 618 women in the control group developed recurrent disease. However, this study was underpowered as it prematurely closed due to decreased enrollment after publication of the results of the Women's Health Initiative in July 2002. Nonetheless, only small incidences of both recurrence and malignancy were found [75].

There are few data on HRT after ovarian cancer. Mascarenhas et al. performed a prospective nation-wide cohort study in Sweden in which 649 women diagnosed with epithelial ovarian cancer (EOC) and 150 patients with borderline ovarian tumors (BOT) were included. Users of HRT after an EOC diagnosis were at a significantly lower risk of dying compared to never users (RR 0.57; 95 % CI 0.42–0.78). The better survival was observed for women with serous tumors and other histological types, but not clearly for women with mucinous or endometrial tumors. For women with borderline tumors there were no associations between HRT use after diagnosis and survival. However, this study was subject to selection bias in prescription of the HRT. Those with better prognosis and younger women may have been more likely to have been prescribed HRT [76]. Although no studies have been published regarding HRT after treatment for granulosa cell tumors of the ovary, the general belief is that it should not be used as it is endocrinologically active and a hormone-dependent disease [77].

A variety of agents are available as an alternative for hormone replacement therapy [78–80]. Progestagens can be effective in controlling hot flushes and night sweats, whereas bisphosphonates, calcium, and vitamin D are used in the prevention and treatment of osteoporosis [79, 81]. Estrogen deficiency may lead to dyspareunia for which vaginal lubricants can be helpful. In women who underwent bilateral oophorectomy, transdermal testosterone turned out to increase the frequency of sexual intercourse and to improve the quality of orgasms. Moreover, ratings on the Brief Index of Sexual Functioning for Women (BISF) rating scale were also improved [82].

In conclusion, existing evidence appears to support the safety of HRT following most endometrial or ovarian malignancies. However, studies are limited and patients should be advised of the paucity of data. For those women with ovarian cancer who are also at increased risk of breast cancer due to inherited gene mutations, the impact of HRT is not known. Continuous combined HRT should be considered in symptomatic patients who are aware of the lack of evidence in this area and considering other risks and benefits of HRT on an individual basis.

HRT After Breast Cancer

Breast cancer is the most common cancer in women affecting up to 1 in 8 [83]. With increasing prevalence and advancing treatments leading to prolonged survival, there are increasing numbers of breast cancer survivors and many women living with the disease [84]. Consequently, treatments for associated morbidities to improve quality of life have become a focus [83]. Menopausal symptoms are prominent in women with breast cancer for a number of reasons including cessation of HRT on diagnosis of breast cancer, chemotherapy-induced ovarian failure, and endocrine treatments (aromatase inhibitors) for estrogen-receptor-positive breast cancers [85]. Menopausal symptoms including hot flushes, night sweats,

sexual dysfunction, and sleep disturbances may be more severe in breast cancer survivors compared to women going through natural menopause [86].

Vasomotor symptoms affect 75 % [87] and are associated with a higher frequency of sleeping difficulties [88]. Vaginal symptoms resulting in atrophic vaginitis affect 50 %, leading to dryness, discomfort, pruritis, dyspareunia, urinary tract infection, and urinary urgency [89, 90]. While hot flushes and sleeping difficulties tend to improve over time, atrophic vaginitis tends to worsen.

Systemic HRT

Estrogen containing HRT is currently the gold standard treatment for vasomotor symptoms at menopause [91]. However, few studies have addressed the safety of HRT in women with a personal history of breast cancer. The HABITS trial (hormonal replacement therapy after breast cancer – is it safe?) was a randomized control trial assessing the efficacy and safety of hormone replacement therapy (decided by treating doctor) after breast cancer treatment. The trial was ceased prematurely after randomizing 434 women and a median follow-up of 2 years, as there was a significantly higher risk of recurrence in those taking HRT, showing a relative hazard of 3.5 with 26 events in the HRT group and 7 in the control group. The risk was highest in those with hormone-receptor-positive cancers (HR 4.8), those not on tamoxifen (HR 3.7), and in those previously on HRT prior to breast cancer diagnosis (HR 6.9). There was no significant difference between combined preparations, estrogen-only preparations, or other forms of HRT including tibolone [92, 93].

The Stockholm trial ran concurrently and was also a randomized control trial assessing HRT in patients treated previously for breast cancer. Despite no increased risk of recurrence in the HRT group, this trial was also ceased prematurely, after randomizing 378 patients, due to difficulty recruiting after HABITS was published [94]. In the Stockholm trial, there were more women using estrogen-only HRT, and it is possible that this may have contributed to the discrepancy in trial outcomes.

The safety and efficacy of tibolone after breast cancer has also been addressed in an international randomized controlled equivalence trial. Over 3,000 women were randomized to tibolone versus placebo. The findings showed that tibolone users were at increased risk of new breast cancers or breast cancer recurrence compared to those using placebo (HR 1.40; 95 % CI 1.14–1.70; $P=0.001$). This adverse effect was more pronounced in those taking aromatase inhibitors after breast cancer (HR 2.42; 95 % CI 1.01–5.79; $P=0.047$). There are insufficient data from HRT or tibolone studies to know if estrogen receptor status influences risk after breast cancer. Consequently, both HRT and tibolone should be avoided in women with a personal history of breast cancer [95].

Vaginal Estrogen and History of Breast Cancer

Symptoms of vulvovaginal atrophy such as vaginal dryness and dyspareunia affect around 40 % of women at menopause. Vaginal symptoms are particularly troublesome in postmenopausal women using aromatase inhibitors or tamoxifen after estrogen-receptor-positive breast cancer. Vaginal estrogen is the most effective treatment for vulvovaginal atrophy [96]. Estrogen preparations can be administered in the form of a vaginal ring, cream, pessary, or a slow-release tablet [84]. Vaginal estrogens have been widely used after breast cancer, and there is no clinical evidence that they impact on prognosis. However, estrogen is absorbed from the vagina into the systemic circulation at low levels. After breast cancer, vaginal estradiol preparations have been shown to increase the quantities of circulating estradiol in women on aromatase inhibitors within 2 weeks of usage [97]. Kendall et al. followed estradiol levels in seven breast cancer survivors on aromatase inhibitors and 25 ug vaginal tablets of estradiol daily for 2 weeks then twice weekly for severe vulvovaginal symptoms. Estradiol levels rose pretreatment from 1.4 to 19.6 pg/mL and deceased to 9.5 pg/mL after 4 weeks of treatment [98]. This raises clinical concerns that vaginal estrogens may prevent the therapeutic action of aromatase inhibitors, which act to reduce circulating estradiol levels by preventing the conversion of androgens to estrogens. A larger study was conducted by Melisko using an intravaginal ring releasing 7.5 ug estradiol over a 24-h period for 12 weeks. The number of patients with elevations in serum estradiol did not reach the prespecified threshold for ceasing the study [99]. From the limited evidence, small retrospective studies indicate that vaginal estrogens do not influence breast cancer recurrence [100].

Vaginal estriol preparations have been shown to be equally as effective as estradiol preparations for the treatment of atrophic vaginitis [101]. Estriol is not as potent as estradiol [102] and cannot be converted to estradiol peripherally. If vaginal estrogens are to be used, estriol (e.g., Ovestin cream) may be a preferable alternative [83].

Concluding Comments

- HRT may lead to a slightly increased risk of ovarian cancer but data are unclear.
- Unopposed estrogens increase the risk of endometrial cancer, and this risk persists for several years after discontinuation of therapy. Ultralow-dose preparations may have a smaller risk but unopposed estrogen therapy cannot be recommended in women

who retain their uterus since there are insufficient safety data. For those who choose to take unopposed therapy, there is no consensus about how to monitor endometrial safety in these women.

- Combined HRT seems to increase the risk of breast cancer and also increases breast density, which is linked with breast cancer risk. It is unclear what duration of combined therapy is required to increase breast cancer risk, but longer duration of therapy is associated with greater risk in postmenopausal women.
- The impact, if any, of estrogen-only HRT on the risk of breast cancer seems limited. The mechanism is not well understood. The only randomized trial on this issue using estrogen-only HRT was underpowered but showed a significant reduction of breast cancer after estrogen-only HRT compared to placebo [103].
- HRT seems to have a positive effect on the quality of life after prophylactic oophorectomy, although presurgical levels of well-being may not be achieved.
- Following endometrial cancer, continuous combined HRT appears to be safe, although data are limited. Similarly, following ovarian cancer, HRT appears to be safe, but estrogen is avoided after granulosa cell tumors. Decisions about HRT use may include consideration of ER and PR status, although there is little evidence to guide these choices.
- In women with a personal history of breast cancer, HRT and tibolone appear to increase the risk of new breast cancers or recurrence and need to be avoided. The safety of vaginal estrogens after breast cancer is not proven. In case of symptomatic need, estriol cream is preferred over local estradiol.
- There is an urgent need to identify safe and effective nonhormonal treatments for menopausal symptoms. All current nonhormonal therapies have been identified from serendipitous observations. Further understanding of the mechanisms underlying vasomotor symptoms is needed to identify new targets for therapy.

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Familial Gynecologic Cancers: Whom to Screen and How to Manage?

24

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Summary Points

- Should all high-grade serous ovarian cancer patients undergo *BRCA1* and *BRCA2* testing?
- Should all endometrial cancer patients undergo tumor testing for Lynch syndrome?
- Should there be consideration of risk-reducing salpingectomy for *BRCA1* and *BRCA2* mutation carriers rather than risk-reducing salpingo-oophorectomy?
- Should screening with CA-125 and transvaginal ultrasound every 6 months be recommended for all *BRCA1* and *BRCA2* mutation carriers?
- Should endometrial biopsy be performed every 1–2 years as screening for women with Lynch syndrome?

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Introduction

Gynecologic cancers are important components of several hereditary cancer syndromes. Identification of individuals who harbor germline mutations in cancer susceptibility genes is important not only for prevention in unaffected family members but also for the cancer patient, in terms of therapeutic implications and prevention of second cancers.

The underlying genetic causes of Hereditary Breast/Ovarian Cancer are germline mutations in *BRCA1* or *BRCA2*. Women with *BRCA1* or *BRCA2* germline mutations have an approximate 40 and 20 % risk of developing ovarian cancer, respectively, and as high as a 85 % risk of developing breast cancer over their lifetime [1–3]. Lynch syndrome includes a hereditary disposition to several cancers, most notably colon, endometrial, and ovarian cancer. Women with Lynch syndrome have an approximate 40–60 % risk of developing colon cancer, a 40–60 % risk of developing endometrial cancer, and a 10–12 % risk of ovarian cancer over their lifetime [4, 5]. Indeed, women with Lynch syndrome often present with a gynecologic cancer as their sentinel cancer and benefit from increased colon screening to prevent a second cancer [6].

While significant strides have been made in the identification of women with Hereditary Breast/Ovarian Cancer and Lynch syndrome, several questions remain in terms of whom to offer genetic testing, how to screen for cancers, and the best way to reduce cancer risk. This chapter addresses these issues from different viewpoints.

Should All High-Grade Serous Ovarian Cancer Patients Undergo BRCA1 and BRCA2 Testing?

We have so far been unable to make a significant impact on the high mortality rate of ovarian cancer, in spite of radical cytoreductive surgery, aggressive chemotherapy, and even population-based screening, including transvaginal ultrasound (TVUS) and/or CA-125 testing [7, 8]. Identification of women who carry *BRCA* germline mutations plays an important

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role in counseling patients regarding disease course, treatment options [9–19], and prevention of second cancers. In addition, *BRCA* testing can impact mortality rates by identifying family members who may also harbor the mutation and have the opportunity to institute prevention measures.

The clinical mainstay of referral for genetic risk assessment has been family history; however, there is increasing evidence that family history criteria may not identify the majority of patients with ovarian cancer who harbor a *BRCA1* or *BRCA2* germline mutation [14]. The unreliability of family history, in terms of both patient reporting and clinical documentation, along with distinct clinicopathologic features that have been identified in *BRCA*-associated cancers, has led to the proposition of several more inclusive strategies for *BRCA* risk assessment. One strategy is universal testing in all ovarian cancers of serous histology, regardless of family history.

Pro

The question of whether all high-grade serous ovarian (HGSOC) patients should undergo *BRCA1* and *BRCA2* testing should be assessed from two viewpoints. Firstly, how the results of this testing will affect the treatment and outcome of the tested patients themselves. We now know from both retrospective and prospective reviews that there is a higher response rate to platinum-based chemotherapy and improved survival in patients with germline *BRCA* mutations. More women with defects in *BRCA1* and *BRCA2* genes have impairment of the homologous-recombination DNA repair pathway, making their tumors susceptible to lethal damage by poly(ADP-ribose) polymerase (PARP) inhibitors [20, 21]. This provides a first opportunity of introducing personalized treatment of ovarian cancer. Patients with *BRCA* mutations showed increased sensitivity to PARP inhibitors through the inability to repair double strand breaks at DNA replication forks [16]. Many studies have also found that a high proportion of ovarian cancers in patients harboring *BRCA* mutations fall into the high-grade serous histologic subtype [13, 14, 22].

The second point of view relates to the ability to identify, through universal testing of all HGSOC patients, family members of the tested patients who are healthy carriers of a mutation. Although genetic predisposition to a variety of cancers has been identified, very few of them have resulted in active measures that will reduce morbidity and mortality. There is therefore a unique opportunity to identify women at very high risk for cancer. Since most genomic scientific discoveries were "lost in translation," we have decided to focus in this chapter on the second aspect, a promising new approach in the clinical application of molecular information. This issue is, in our opinion, of significant importance and opens the door to the field of preventive medicine, in which gynecologic oncologists are currently less active and should become key contributors. This relatively new strategy represents another dimension to our efforts to reduce mortality from ovarian cancer.

In the new era of medicine, i.e., personalized cancer prevention, the goal is to identify people with a genetic profile that increases their risk of developing cancer, ovarian cancer specifically, for which we have effective prevention strategies. The arguments in favor of mutation testing for all HGSOC as part of a preventive strategy are based upon two important evidence-based observations:

(a) The chance of identifying a deleterious mutation in *BRCA1* and *BRCA2* in this unselected group of patients is high and approaches 25 % [23–25].
(b) The ability to apply the information obtained from the identification of the tested positive patients to their family members and offer them highly effective prevention measures is feasible [26].

Two important publications of the recent year present data on mutation frequency among HGSOC patients. Walsh et al. [23, 24] analyzed 360 ovarian cancer patients for mutations in *BRCA1 or BRCA2* and or other less common cancer-predisposing genes. They found overall deleterious mutations in 82 women (23 %). When HGSOC were evaluated separately, they found 25 % mutations in *BRCA1or BRCA2*. Interestingly, if only patients of young age or with significant family history had been tested, rather than unselected ovarian cancer patients, 30 % of these carriers would have been missed.

Another publication from Schrader et al. [25] on a series of 131 HGSOC patients similarly found 25 % (26 patients) to harbor a germline mutation in either BRCA1 or BRCA2. They also concluded that all HGSOC should be tested since by using current referral guidelines, 25 % of mutation carriers would have been missed. With this information at hand and with careful genetic counseling, one can identify, through testing of HGSOC patients, the family members who are carriers and propose a preventive strategy that can effectively reduce mortality from this highly malignant disease.

Our experience in the high-risk Ashkenazi Jewish patients was even more impressive, and mutations were identified in 40 % of HGSOC patients. In the Ashkenazi Jewish population, 2.5 % are carriers of one of three common founder mutations in BRCA1 or BRCA2 (common Jewish mutations, CJM). Therefore, we have adopted the policy of testing all our ovarian cancer patients CJMS, regardless of family history [27]. This approach has been very important to female relatives of our patients who were found to be carriers as a result of this testing policy. While the costs are reasonable and false-positive results nonexistent, identified carriers can plan their preventive measures.

As *BRCA1* and *BRCA2* sequencing for deleterious mutations becomes more frequently performed and less costly, we will identify a variety of new deleterious germline mutations and also many variants of undetermined significance (VUS)

in populations of patients with no known founder mutations. The latter will create a major obstacle in genetic counseling and decision-making. Many of these VUS actually have insignificant clinical implications, and one should be fully familiar with the data regarding their impact on disease initiation in order to avoid unnecessary actions made by carriers of VUS due to anxiety and fear. As more information on this problem accumulates and is made available to physicians and genetic counselors, we expect to minimize this drawback of testing all HGSOC patients [28, 29].

Three acceptable and proven modalities for prevention of ovarian cancer include:

(a) Prolonged oral contraceptive use for younger women
(b) Surgical intervention with risk-reducing salpingo-oophorectomy (RRSO) for women who have completed childbearing
(c) Pregestational genetic diagnosis (PGD) for carriers who desire reproduction and wish to avoid the transfer of the mutation to their offspring

A large body of evidence shows that the prevention of ovulation for a prolonged period of time (>5 years) reduces the risk of ovarian cancer by close to 50 %. This observation holds for *BRCA1 and BRCA2* mutation carriers as well. In addition RRSO has been shown to be highly effective in preventing ovarian cancer and prolonging life [26].

Preventive measures can be extended further to PGD, in which embryos created through in vitro fertilization (IVF) can be analyzed for their carrier status, and only embryos that are non-carriers (or male carriers in some situations) transferred. Although prevention of a newborn carrier could be achieved by prenatal diagnosis of fetal cells (amniocentesis or chorionic villi biopsy), PGD has been generally better accepted by young couples as a modality for preventing the transfer of a BRCA mutation from parent to child.

The testing policy we support here follows the famous statement made by the great American leader, Benjamin Franklin (1706–1790), "An ounce of prevention is worth a pound of cure." With the introduction of personalized preventive medicine strategy to our practice, by testing all HGSOC patients, we can identify relatives at risk, with a relatively low cost (which is further decreasing constantly), and actually prevent a malignant disease from developing while reducing all medical expenses required in the surgical and supportive medical treatments devoted to patients eventually diagnosed with ovarian cancer.

Con

Approximately 10–15 % of women diagnosed with epithelial ovarian cancer harbor a germline mutation in *BRCA1* or *BRCA2* [22, 30–32]. Conversely, 85–90 % of women are diagnosed with sporadic ovarian cancer. The main argument against BRCA testing in all high-grade serous ovarian cancer patients stems from the cost-effectiveness of this strategy, given that the majority of patients with ovarian cancer will not carry a germline mutation. Kwon et al. performed a cost-effectiveness analysis of four strategies to identify patients for BRCA testing [33]. The four strategies included no BRCA testing, BRCA testing if patients met guidelines published by the SGO (Table 24.1), BRCA testing for invasive serous cancers, and BRCA testing for any invasive epithelial ovarian cancer. The only strategy that was considered cost-effective, defined as an incremental cost-effectiveness ratio (ICER) less than $50,000, was to test women who met SGO guidelines by family history, which resulted in an ICER of $32,018 (Table 24.1). Testing women with invasive serous cancer gave an ICER of $128,465, compared to an ICER of $148,363 for testing women with any invasive epithelial cancer. Certainly, if the cost of genetic testing decreases, the cost per life year saved will be impacted.

Table 24.1 Cost-effectiveness analysis of testing strategies in BRCA

Strategy	ICER (cost per year of life gained)	Average life expectancy gain
No testing	–	–
SGO criteria	$32,018	+12 days
All invasive serous cancers	$128,465	+4 days
All invasive epithelial cancers	$148,363	+3 days

Adapted from Kwon et al. [33]
Strategy defined as cost-effective if ICER <$50,000

The idea of histology-based referral for genetic testing in BRCA has also been addressed in breast cancer [34]. The most inclusive strategy determined by a cost analysis was testing women with triple negative breast cancer diagnosed at age less than 50. Unfortunately, using an age cutoff is less effective for ovarian cancer as many patients, specifically patients that carry a germline *BRCA2* mutation, are diagnosed with cancer at age greater than 60 [1, 31, 35].

The Society of Gynecologic Oncologists (SGO) published guidelines in 2007 [36], outlining who should be referred for possible genetic testing. Most of the criteria are based on family history of breast and ovarian cancer. Two groups were identified, those with a 20–25 % risk and those with a 5–10 % risk of inheriting a germline mutation, placing them at increased risk for developing breast or ovarian cancer (Table 24.2). Patients with a 20–25 % risk are recommended to have genetic risk assessment, including genetic counseling and genetic testing if indicated. Several cautionary notes were highlighted in these guidelines, including the consideration of adoption, paucity of female relatives, and early hysterectomy or salpingo-oophorectomy in female relatives. These guidelines are the result of consensus opinion and have not been validated in a prospective study. One concern is the potential lack of sensitivity of these guidelines for

Table 24.2 SGO criteria for hereditary breast/ovarian cancer

Patients with 20–25 %	Patients with 5–10 % risk
Women with personal history of both breast and ovarian[a] cancer	Women with breast cancer ≤40 years
Women with ovarian cancer[a] and a close relative[b] with breast cancer at ≤50 or ovarian cancer at any age	Women with bilateral breast cancer (particularly if first cancer was ≤50 years)
Women with ovarian cancer[a] at any age who are of Ashkenazi Jewish ancestry	Women with breast cancer ≤50 years and a close relative with breast cancer ≤50 years
Women with breast cancer ≤50 and close relative[b] with ovarian[a] cancer or male breast cancer at any age	Women of Ashkenazi Jewish ancestry with breast cancer ≤50 years
Women of Ashkenazi Jewish ancestry and breast cancer ≤40	Women with breast or ovarian cancer at any age and ≥2 close relatives with breast cancer at any age
Women with a first- or second-degree relative with a known BRCA1 or BRCA2 mutation	Unaffected women with a first- or second-degree relative that meets one of the above criteria

Adapted from Lancaster et al. [36]
[a]Peritoneal and fallopian tube cancer should be included in the spectrum of Hereditary Breast/Ovarian Cancer Syndrome
[b]Close relative = first-, second-, or third-degree relative

identifying the majority of *BRCA1 or BRCA2* carriers, as they are heavily based on family history. A recent prospective study reported that as many as 44 % of patients with a *BRCA1* and *BRCA2* germline mutation did not report a family history of breast or ovarian cancer [14]. Certainly universal testing of all ovarian cancers of serous histology would increase the number of mutation-positive ovarian cancer patients.

While *BRCA1* and *BRCA2*-associated ovarian cancers are commonly high-grade serous, other histologies have been reported, including endometrioid, clear cell, transitional cell, and carcinosarcomas [23, 30, 31]. Indeed, in the analysis by Kwon et al. including all epithelial ovarian cancers increased the adjusted life expectancy at a similar rate with minimal increase in the cost per year of life gained over testing serous cancers alone.

As the cost of genetic testing declines, universal testing may become a viable option. Refining clinical criteria, such as the SGO criteria, for genetic testing referral remains the most cost-effective option.

Should All Endometrial Cancer Patients Undergo Tumor Testing for Lynch Syndrome?

Lynch syndrome (LS) is the most common cause of hereditary endometrial cancer (EC), accounting for 2–5 % of all EC [37]. It is characterized by autosomal dominant inheritance with penetrance of 85–90 % for an LS-type cancer (colorectal, endometrial, urinary tract, and others) [38]. The underlying molecular mechanism is a germline mutation in one of the four mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2), causing cancer susceptibility due to MMR deficiency. Women with LS have a considerable lifetime risk of developing EC that equals to or even exceeds that of colorectal cancer (CRC) [4]. In LS individuals who have both a gynecologic and a GI malignancy, gynecologic cancer was the sentinel malignancy in approximately 50 % of these women [6, 39].

Historically, referral for genetic counseling and germline testing for LS has been based largely on family history and age at diagnosis in the CRC population. These factors are reflected in the two sets of clinical criteria used to identify patients at increased risk of carrying a germline mutation, the Amsterdam criteria and Bethesda guidelines.

There are many important implications for diagnosing LS in EC patients: initial management, prevention of second LS cancers, and for identification of family members at risk. Strategies for prevention and early detection of colon cancer and other LS cancers have been defined. However, the optimal method for identification of LS in women who present with EC is uncertain.

Pro

Given the fact that EC carries a significant portion of the cancer burden for women with LS, both the 1991 Amsterdam criteria and the 1997 Bethesda guidelines have been revised to include EC (Table 24.3) [40, 41]. In addition, the SGO education committee published a series of guidelines in 2007 aimed to help direct referral for genetic assessment in patients at increased risk for LS. These guidelines defined two groups of patients, those with a 20–25 % risk and those with a 5–10 % risk of having a genetic predisposition to cancer. Patients at higher risk are recommended for genetic assessment, while patients with a 5–10 % risk are defined as a group where genetic assessment may be helpful (Table 24.4) [36].

While the SGO guidelines are more inclusive than Amsterdam II criteria and the revised Bethesda guidelines, these recommendations are based largely on expert opinion and have never been tested prospectively in an endometrial cancer population. Indeed, the SGO criteria continue to be based mainly on a family history of Lynch-associated cancers and diagnosis at age less than 50, when numerous studies have shown that many patients do not have a significant family history

Table 24.3 Lynch syndrome criteria

Amsterdam II criteria	Revised Bethesda guidelines
There should be at three relatives with an HNPCC-associated cancer colorectal cancer (CRC), endometrial, small bowel, ureter, renal pelvis	CRC diagnosed in a patient who is less than 50 years of age
One should be a first-degree relative of the other two	Presence of synchronous, metachronous CRC, or other HNPCC-associated tumors, regardless of age[a]
At least two successive generations should be affected	CRC with the MSI-H-like histology diagnosed in a patient who is less than 60 years of age
At least one should be diagnosed before 50	CRC diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under 50 years of age
Familial adenomatous polyposis should be excluded	CRC diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age
Tumors should be verified by pathologic examination	

[a]HNPCC-related tumors include CRC, endometrial, stomach, small bowel carcinoma, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain tumors (glioblastoma as in Turcot syndrome), sebaceous gland adenomas, and keratoacanthomas (Muir-Torre syndrome)

Table 24.4 SGO criteria for Lynch syndrome

Patients with 20–25 % risk	Patients with 5–10 % risk
Patients with endometrial or CRC who meet the revised Amsterdam criteria (as above)	Patients with endometrial or CRC diagnosed prior to age 50
Patients with synchronous or metachronous endometrial and CRC with the first cancer diagnosed prior to age 50	Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch-/HNPCC-associated tumor at any age
Patients with synchronous or metachronous ovarian and CRC with the first cancer diagnosed prior to age 50	Patients with endometrial or CRC and a first-degree relative with a Lynch-/HNPCC-associated tumor diagnosed prior to age 50
Patients with CRC or endometrial cancer with evidence of a mismatch repair defect (microsatellite instability or immunohistochemistry with loss of expression of MLH1, MSH2, MSH6, or PMS2)	Patients with CRC or endometrial cancer diagnosed at any age with two or more first- or second-degree relatives with Lynch-/HNPCC-associated tumors, regardless of age
Patients with a first- or second-degree relative with a known mismatch repair gene mutation	Patients with a first- or second-degree relative that meets the above criteria

Adapted from Lancaster et al. [36]

of Lynch-associated cancers and are diagnosed over the age of 50 [37, 42, 43]. In a 2006 study of over 500 endometrial cancers, only 30 % of patients found to carry a germline Lynch mutation met published criteria for genetic testing by family history and only 40 % of patients were diagnosed at age less than 50, suggesting that 60–70 % of Lynch cases might be missed by using the current guidelines [37].

In addition, pathologic features have been suggested as an additional triage method for identifying patients who should be referred for genetic testing, including tumor involving the lower uterine segment, presence of tumor infiltrating lymphocytes, and peritumoral inflammation [44, 45]. But these have never been evaluated in a rigorous fashion and are not found consistently in Lynch-associated endometrial cancers [46]. While these features may raise suspicion for LS when seen in endometrial cancer cases, they do not occur reliably enough to be used as criteria for testing EC patients for LS.

As clinical criteria and pathologic features are not consistently reliable in identifying patients who are at risk for LS, many authors suggest universal screening of all endometrial cancers for Lynch-associated MMR defects [47]. Universal screening has been implemented in the colorectal cancer population using reflex or automatic tumor testing. Universal screening in these patients not only identifies patients and other family members who are at increased risk of Lynch-associated cancers but has treatment and prognostic implications [48]. Reflex testing refers to routine testing performed by a pathologist without specific clinician request. Clinical criteria (other than age) are not included in reflex testing strategies, as the pathologists are usually unaware of these criteria. Reflex testing for LS using MMR immunohistochemistry (IHC) and/or microsatellite instability (MSI) analysis in all CRC patients is an emerging standard of care. Some groups have similarly recommended reflex MMR testing in EC patients, either for all EC cases or for EC patients under 50 years of age [44].

In the CRC population, MMR protein expression by IHC and MSI analysis has been shown to have a high concordance, and IHC has the advantage of directing germline testing, has a lower cost, and is readily available at most hospitals. Cost-effective analyses have shown that universal

screening with IHC on all newly diagnosed colon cancers has a favorable incremental cost-effectiveness ratio when compared to initial screen with MSI analysis [49].

While the use of reflex testing in EC is suggested by some authors, the method of screening is not as clear. Most algorithms include screening of all cancers with MSI analysis, IHC, or both [42, 43, 50]. If a tumor is found to be MSI high or has loss of one of the Lynch-associated MMR proteins on IHC, then the patient is referred to genetic counseling for further risk assessment and germline testing. As a majority of defects found in MLH1 are due to epigenetic hypermethylation of the MLH1 promoter, many studies also include an intermediate step of hypermethylation analysis for tumors with loss of MLH1 [43]. IHC has all the advantages outlined in CRC and has been shown to also have high concordance rates with MSI analysis in endometrial cancer as well [43]. Thus, one possible algorithm could include reflex IHC on all newly diagnosed endometrial cancers with hypermethylation analysis in cases where loss of MLH1 is found on initial IHC.

To date, there have been two prospective evaluations of population-based screening for LS in endometrial cancer, one including IHC alone without hypermethylation analysis [42] and one including MSI, IHC, and hypermethylation analysis [43]. Backes et al. evaluated 140 cases of endometrial cancer by IHC alone and found that 21 % of patients had absent staining for at least on MMR protein; however, the majority of cases (24/30) were due to loss of MLH1 or PMS2. Patients were referred to genetic counseling if they had loss of MSH2/MSH6 or had loss of MLH1/PMS2 at age less than 60 or family history of Lynch-associated cancers. Unfortunately, only one patient went through with germline testing, which was negative [42]. Leenen et al. evaluated 179 cases with IHC, MSI, and MLH1 hypermethylation assay when necessary. Forty-two cases were classified as MSI high with at least one MMR protein absent on IHC; however, 31 were found to have hypermethylation in MLH1, leaving 11 cases with likely Lynch syndrome (6 %). Ten of these patients underwent germline testing with a mutation in MSH6 found in 6 patients and a mutation in PMS2 found in 1 patient. Interestingly, in the 10 patients found to have likely LS, only 2 patients met Amsterdam criteria and 3 patients met revised Bethesda guidelines, suggesting that universal tumor testing is superior to family-history-based referral [43].

A recent study by Kwon et al. carried out a cost-effectiveness analysis for several strategies to help identify endometrial cancer cases with likely LS. IHC of tumor specimens for patients with a first-degree relative with a documented Lynch-associated cancer was the most cost-effective strategy [51]. Unfortunately, many patients do not report even a first-degree relative with a significant family history. Only two patients in the study by Leenen et al. reported a first-degree relative with a Lynch-associated cancer. This would omit the majority of other cases found to have likely LS on IHC from the opportunity for germline testing [43].

While family history, age at diagnosis, and pathologic features are all components of a patient's history that can help raise clinical suspicion for LS, none of these factors alone are reliable enough to use as criteria for tumor testing. Universal screening, with IHC or MSI, can increase the detection of Lynch-associated endometrial cancer and prevention of secondary cancers, most notably colorectal cancer. Further studies are needed to help characterize the most useful and cost-effective algorithm to use for universal tumor testing.

Con

Current methods (clinical history and tumor morphology) to predict MMR deficiency in patients with EC are suboptimal [52] and less refined than for patients presenting with CRC. Specificity of these methods in the setting of unselected patients with EC remains poorly described. There are few studies of LS EC, with variable study designs, recruitment strategies, and definitions. The 2010 Jerusalem LS consensus workshop recommended that all CRCs in patients under 70 years be screened for MMR by tumor testing; however, the statement regarding EC was merely "it should be considered" [53].

MMR status is increasingly utilized as a prognostic, predictive, and possible LS biomarker in CRC. Tumor testing is a step which prompts molecular studies for germline mutations in genes related to LS, as molecular testing is labor intensive and expensive. With the advent of next generation sequencing (NGS), in the near future it is likely that EC patients will undergo direct molecular testing for mutations in LS genes, as testing will become more widely available, quicker, and less costly. Therefore, the discussion on tumor testing is likely very soon to be less relevant. However, even in the era of NGS, the problem of incomplete penetrance [54] and interpretation of test results will be issues complicating molecular testing, and therefore practical and ethical issues that we raise will still be applicable.

At present time, the optimization of LS screening for EC patients needs prospectively gathered data to provide evidence in favor of any particular detection method, as screening criteria have not been validated or implemented comprehensively. With limited evidence of yield of reflex tumor testing in EC, the uncertain quality of the test, and ethical aspects yet to be adequately addressed, implementing tumor screening for LS in all EC patients may be premature. Optimal algorithms for the detection of LS in EC patients are vague and practice varies. Family/personal medical history and tumor morphology/topographic location usually serve as the initial criteria for LS investigation, followed by tumor testing when criteria fulfilled, with subsequent germline testing when tumor tests positive.

The traditional clinical screening schemas for LS in CRC, Amsterdam and Bethesda, perform poorly in EC patients

[37, 46] as they fail to identify >60 % of LS-associated EC. The Society of Gynecologic Oncology (SGO) has presented alternative schemas focused on EC patients, with higher sensitivity than the traditional schemas in identifying (71–93 % vs. 36–58 %, respectively). However, their specificity is untested for EC, and they involve detailed pedigree drawing by genetic counselors [46].

In a recent cohort, the mean age at presentation with EC was 49.3, 46 and 50.6 years for patients who had MSH1, MLH2, and MSH6 mutations, respectively [46]. Additional studies have also shown that EC in patients with MSH6 mutations tend to occur over 50 years (8) and 60 % of mutations in LS EC patients are in MSH6 [37]. Consequently, restricting LS screening to patients with EC aged <50 years would fail to detect many LS cases.

Some studies suggest a higher incidence of non-endometrioid EC [55] in LS patients than in sporadic EC, while others did not support this. Certain histologic features, including tumor infiltrating lymphocyte and peritumoral inflammation, high-grade tumors, and location of EC in the lower uterine segment, have been shown to correlate with LS in some studies on patients with EC [55, 56]. However, additional studies have refuted these features as predictors [57].

Thus, family history, age of patient, and morphologic features are not adequately sensitive and/or specific to detect LS EC, and restricting LS screening to these parameters should not be recommended.

The College of American Pathologists (CAP) advocates that pathologists recommend MMR testing in tumors associated with LS; however, it acknowledges that MSI in EC is less well characterized than in CRC [52].

In the largest prospective study on EC LS to date, which included 543 unselected EC patients, the sensitivity of MSI for LS was 90 % [37], in accordance with some later studies (e.g., 92 % reported by Mercado) [58]. However, a high proportion of LS patients with EC have mutations in MSH6 [37], and in these patients, the sensitivity of MSI is reported to be only 77 %. This is different from the MSI findings in CRC with LS, in which mutation carriers do not have MSI-low tumors [59].

In addition, specificity of MSI for LS is only 78 % and positive predictive value (PPV) about 9 % for all EC cases [58]. In a study on EC patients <age 50, PPV of MSI was only 32 % for LS [60]. Up to 30 % of *sporadic* (non-LS related) ECs have MSI, due to methylation of the MLH1 promoter [46]. Whereas in CRC negative somatic BRAF mutation is helpful in excluding other causes of MSI, there is no analogous test to exclude other causes of MSI in EC, hereby limiting the specificity for LS when an EC shows high MSI. Therefore, at this time, it does not seem reasonable to perform MSI as a reflex test in EC, due to its low sensitivity and specificity.

In two recent studies, there was discordance between MSI and IHC in 15.8 and 11.8 % of EC cases that were tested by both methods [46, 61]. This advocates against the sole use of IHC. IHC has a sensitivity of 80–95.7 % for LS in EC in different reports [37, 46, 58]; however, some of these are based on a small number of cases. Specificity of IHC for LS is 67–88.8 % [58, 59] and PPV is 10 %. In the cohort of 100 EC patients under age 50, PPV was 38 % [60]; two women had MSI-H tumors in addition to abnormal IHC but did not have a germline LS mutation. One conclusion of the latter study was that there are cases in which tumor studies are inconclusive or are not consistent with germline test results.

Sporadic tumors may have abnormal IHC (i.e., absence of protein staining but without germ line mutations) due to a false IHC staining result, promoter methylation, or presence of biallelic somatic mutations in the tumor.

Ethical issues around reflex MMR tumor testing are currently unresolved, mainly due to patient informed consent being the ethical principle of patient autonomy. For some patients, psychosocial risks of positive tumor MMR testing may be an issue, and guidelines on patient consent are crucial prior to implementing MSI/IHC as a reflex test. It may be important to prepare patients and their families for the possibility of a positive screening test and the accompanying recommendation that MMR gene sequencing be considered [62].

MSI involves the direct analysis of DNA and is consistent with the definition of genetic testing as "an analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes" [62]. In line with this definition, MSI may be regarded as requiring patient consent. However, debates about MSI screening for LS have not given rise to practical guidelines on the need to obtain patient consent.

Unlike MSI screening, which characterizes the tumor without providing genetic information about the patient, IHC can provide specific genetic information about the patient and the patient's family. Because IHC screening can predict the presence of an inherited mutation in a specific gene, IHC has aspects in common with most genetic tests, including characteristics which may increase psychosocial risk and necessitate patient consent. In contrast to MSI screening, a positive IHC test suggests that not only one of the MMR genes is mutated but also *which* MMR gene is implicated [62]. Further study to define the level of perceived risk (or actual harm) associated with IHC testing and to assess the risk benefit ratio is necessary before a recommendation of informed consent can be supported.

Some authors [62] claim that MSI and IHC should not be considered germline tests, as positive testing is only suggestive of heritable MMR mutation and not considered diagnostic. A clinical recommendation by the Jerusalem workshop suggested that MMR tumor testing should not be considered genetic testing [53].

However, MMR testing has similarities with other genetic analyses for which informed consent is typically required. The Centers for Disease Control and Prevention panel on the Evaluation of Genomic Applications in Practice and

Prevention Working Group has recommended "With limited benefit of genetic testing to the CRC patient, informed consent should be obtained before MSI or IHC testing" [63].

Reflex testing is a strategy that requires more evidence of clinical yield, cost-benefit analysis, proficiency tests to ensure technical quality, test standardization and clinical coordination, and a consensus to resolve ethical issues prior to implementing it as a screening test in all EC cases.

Should There Be Consideration of Risk-Reducing Salpingectomy for BRCA1 and BRCA2 Mutation Carriers, Rather Than Risk-Reducing Salpingo-Oophorectomy?

Screening for ovarian cancer in *BRCA* mutation carriers has shown disappointing results, with no current screening guidelines that have been shown to decrease late stage diagnosis and, as a result, mortality [64, 65]. Consequently, RRSO is used to decrease the risk of ovarian, fallopian tube, primary peritoneal, and breast cancer in *BRCA* mutation carriers by 80–96 and 50 %, respectively [26, 66, 67]. Current guidelines recommend RRSO between the ages of 35 and 40 years following completion of childbearing, with individual consideration for age of diagnosis of ovarian cancer in previous family members [68].

Review of RRSO specimens in *BRCA* mutation carriers has shown occult cancers in the fallopian tube, ovary, as well as peritoneal washings in approximately 2.5–14.6 % of specimens [69–74]. The observation that the majority of these occult cancers in *BRCA* mutation carriers are found in the fallopian tube led to the development of a new model for serous carcinogenesis in ovarian cancer, with cancers defined as type I and II tumors [75–78]. Type II cancers represent high-grade serous, endometrioid, undifferentiated carcinomas, and carcinosarcomas, including *BRCA*-associated ovarian cancers. These cancers are thought to arise in the distal fimbria of the fallopian tube with implantation on the ovarian surface where dominant tumor growth occurs [78].

Risk-reducing salpingectomy without oophorectomy (RRBS) has been proposed as an alternative to RRSO given the discovery of carcinogenesis within the distal fallopian tube. This could be advantageous for several reasons, most importantly because it could avoid early menopause at the time of prophylactic surgery and the resultant downstream medical effects [77]. Early menopause has been associated with decreased bone mineral density, increased risk for coronary heart disease and stroke, and increased cognitive impairment and dementia [79–86]. Many of these risks can be decreased with the addition of estrogen replacement following surgical menopause [79, 80]. Unfortunately, not all women are candidates for hormone replacement therapy, specifically if they have a history of hormone-positive breast cancer.

Pro

The recently published studies in which the pathophysiological origin of ovarian and peritoneal serous cancer comes from a series of premalignant, genetic, molecular events in the fallopian tubes have been stimulating scientifically and challenging clinically [87]. In principle, the phenomenon, which was studied carefully and correlated with histological analysis, identifies precancerous lesions in the fallopian tubes of *BRCA1* and *BRCA2* mutation carriers, which eventually lead to the rapid development of ovarian cancer. Although this evolutionary explanation for ovarian cancer is questioned by some opposing researchers, it may very well be the initial step of carcinogenesis in many, though not necessarily all, BRCA mutation carriers.

Following these observations and research, it is quite tempting to propose a risk-reducing surgical procedure for younger women, who wish to maintain their ovaries in vivo, by removing only their fallopian tubes with RRBS. This approach was already proposed in the literature [88].

When evaluating this controversial issue, one should consider two opportunities in which RRBS could be advocated:

(a) In the young mutation carrier who wishes to maintain fertility and in which this procedure is a first step meant to care for the transition period to be followed by risk-reducing bilateral oophorectomy upon completion of childbearing. Obviously these women should be counseled as for the need for IVF-ET with or without PGD.
(b) As the only risk-reducing procedure, either throughout life or until the age of natural menopause.

Current data and follow-up studies are not available at present to confirm the preventive value for RRBS. Unfortunately, we may never have a high level of evidence to support this approach, yet there are women who may benefit from it. At the present time and with the limited information available, it is our belief that RRBS should be proposed to the younger carrier, with a family history of very early onset of ovarian cancer, on the one hand, yet still planning her family and childbearing on the other hand.

Specifically in those women who are considering PGD, which involves IVF-ET, the presence of the FT is not necessary for reproduction, and their removal will not affect fertility. We have recently performed RRBS in a 33-year-old carrier of a BRCA1 mutation whose mother died at the age of 34 due to ovarian cancer. The woman was planning a last pregnancy with IVF-PGD and plans to complete the RR-BO postpartum.

Con

While risk-reducing salpingectomy is an attractive alternative to RRSO, there have been no studies to evaluate the efficacy of salpingectomy alone in the reduction of ovarian,

fallopian tube, or primary peritoneal cancer risk. There is no objective evidence that the substantial risk reduction seen with RRSO would be translated to risk-reducing salpingectomy. While the majority of occult cancers are found in the fallopian tube, there are still documented cancers found in the ovary and in peritoneal washings [69].

Another potential drawback of risk-reducing salpingectomy is the unknown impact on breast cancer risk. Current studies show that breast cancer risk is reduced by approximately 50 % following RRSO [26, 66, 67]. This risk reduction is greatest when RRSO is performed prior to natural menopause, with one study showing the greatest effect when RRSO was performed prior to age 40 [89, 90]. The impact that risk-reducing salpingectomy would have on this risk has to date not been explored and is an important benefit of RRSO [88].

The addition of oophorectomy either a few years following risk-reducing salpingectomy or after completion of menopause also raises several concerns. First, the addition of a second procedure adds to the surgical risk for the individual patient. Second, if oophorectomy shows the greatest benefit prior to menopause in terms of breast cancer prevention, the time span between these two procedures may be very short. It is unknown if this small window of time would substantially help decrease the medical and quality of life issues associated with surgical menopause. Third, patients may prolong the time from salpingectomy to oophorectomy, decreasing the benefit of oophorectomy in breast cancer prevention [88]. Finally, the addition of a second procedure may decrease patient compliance to some extent, with some women opting not to have an oophorectomy following salpingectomy. Additional studies regarding the impact and treatment of surgical menopause are needed in BRCA mutation carriers to help further understand the long-term effects of RRSO at a young age and to develop alternative therapies that could combat these effects.

Should Screening with CA-125 and Transvaginal Ultrasound Every 6 Months Be Recommended for All BRCA1 and BRCA2 Mutation Carriers?

Women who carry germline mutations in *BRCA1* and *BRCA2* have an approximate 40 and 20 % risk of developing ovarian cancer, respectively, over their lifetime [1–3]. Given this increased risk, several strategies have been investigated to help reduce the incidence of and mortality associated with ovarian cancer, including screening, chemoprevention, and prophylactic risk-reducing salpingo-oophorectomy (RRSO). Current screening guidelines recommend transvaginal ultrasound as well as serum CA-125 every 6 months starting at age 30 or 5–10 years prior to the earliest cancer diagnosis in a family member [68].

Pro

Both transvaginal ultrasound and CA-125 have inadequacies when used alone in ovarian cancer screening, especially when applied to premenopausal women. While transvaginal ultrasound has the advantage of detecting masses in the ovary, a large number of benign lesions may be discovered, leading to a high number of unnecessary procedures [91]. In addition, prospective studies including only high-risk women have failed to diagnose invasive cancers at an early stage, even with transvaginal ultrasound and pelvic exam every 6 months [92]. CA-125 levels can be affected by many factors including benign diseases such as endometriosis, age, race, history of breast cancer, smoking, and use of hormone therapy [93, 94]. In an effort to improve the specificity, sensitivity, and positive predictive value of these two modalities, combined screening has been used in both the general and high-risk population in clinical trials.

Studies to date have shown screening with transvaginal ultrasound and traditional CA-125 measurements to be ineffective at diagnosing cancers at an early stage. As a result, mortality associated with ovarian cancer in screening populations has not changed [91, 95–98]. Hermsen et al. showed development of interval cancers in *BRCA* mutation carriers who were screened annually with the majority diagnosed at a late stage [95]. The recently published results of phase I of the UK Familial Ovarian Cancer Screening Study (FOCSS) showed a sensitivity of 81–87 % and a positive predictive value of 25 % in diagnosing incident cancers in women with at least a 10 % risk of ovarian cancer. Unfortunately, only 2/13 of incident cancers were stage I, once again highlighting the need for more frequent screening in this high-risk population [97]. This study did move to a phase 2 with screening every 4 months, with follow-up data still pending. The Gynecologic Oncology Group (GOG) also performed a study, protocol 199, to answer this question; however, the long-term follow-up of these patients is not yet known [99]. Women included in this study included *BRCA1* and *BRCA2* mutation carriers as well as women at high risk based on family history. Patients either underwent RRSO or had screening with CA-125 and transvaginal ultrasound every 6 months with a 5-year follow-up period.

As traditional CA-125 measurements have shown disappointing results in clinical trials, there has been an evolution in the use of CA-125 in screening. Instead of using a single value with a defined cutoff for normal values, recent studies have used the slope of CA-125 values over time in the individual patient. This approach, entitled the Risk of Ovarian Cancer Algorithm (ROCA), uses the change in the slope of CA-125 with transvaginal ultrasound as a second step if the ROCA score puts a patient at increased risk for ovarian cancer [100]. This method was applied prospectively to population-based screening in 6,682 women with a specificity of 99.8 % and positive predictive value of 19 %. Three

invasive cancers were found in this study, with all three being early stage [101]. The ROCA method is also being applied to the high-risk population enrolled in GOG 199. This will be the first application of ROCA in a high-risk population. These results will be equally important as many of the patients enrolled in GOG 199 are premenopausal, where CA-125 levels are known to be more unreliable [102]. All the studies to date that have used the ROCA method have included postmenopausal women in the general population. While this method is still under evaluation, it shows forward movement in thinking and application of tools that we currently have to help improve the efficacy of ovarian cancer screening.

Unfortunately, there is a paucity of prospective, large-scale data for screening every 6 months with transvaginal ultrasound and serum CA-125 level in the high-risk population that includes *BRCA1* and *BRCA2* mutation carriers. More specifically, there is a lack of data in high-risk patients using the ROCA method. Until these questions are answered, the best recommendation for women with germline BRCA mutations prior to RRSO or for women who choose not to undergo RRSO is screening with CA-125 and ultrasound every 6 months. Patients do need to understand the drawbacks of our current screening methods, especially when considering RRSO.

Con

Once identified as carriers of a *BRCA* mutation, women expect the medical system to provide them with a reliable and meaningful "alarm system" that screens and detects premalignant or early malignant ovarian tumors. Obviously the fear of ovarian cancer, which many of them witnessed with a family member, is high and provokes serious anxiety. We as medical providers are supposed to explain properly and give directions on the availability of screening options. Unfortunately, all large-scale studies of screening for ovarian cancer in the general population have failed to show a significant success. Publication of the largest study even on this matter led by Jacobs et al. in the UK involving 200,000 women will appear in 2015.

Nevertheless, it was expected that in the high-risk population of carriers, these screening modalities, i.e., CA-125 and TVS, would be more effective. Few studies have related specifically to screening of high-risk population, and the only possible advantage to screening was a slight shift in stage in favor of earlier stage at diagnosis in the screened group as compared with the non-screened [103].

We have recently encountered a 39-year-old patient who was followed in our special carrier's clinic for several years. At the age of 38 she conceived and was followed up regularly with US. Two months following a normal delivery and several screens, she presented with advanced stage bulky ovarian cancer with massive ascites. This case report is only intended, once again, to reflect the natural course of ovarian cancer which can develop within weeks so that screening tests performed every 6 months can easily miss the disease. In addition, CA-125 can be extremely misleading in the reproductive age due to physiologic and non-malignant elevations which are false-positive and may provoke anxiety and unnecessary action.

Unlike the general population, one cannot counsel carriers to "do nothing" until they reach the age suitable for RRSO. However, given the fruitlessness of screening by TVS and CA-125 for early detection of ovarian cancer among carriers, one should thoroughly explain to the carrier the serious limitations of current screening methods and the meaning of positive findings. It may be difficult to persuade women to avoid screening, but educating them about the limited value of such screening is our obligation.

Should Endometrial Biopsy Be Performed Every 1–2 Years as Screening for Women with Lynch Syndrome?

Patients with LS carry a 42–60 % lifetime risk of developing endometrial cancer, exceeding the risk for colorectal cancer [4, 5] and highlighting the need for surveillance in this patient population for cancer prevention or early detection. As the incidence of endometrial cancer as a part of LS has become increasingly evident, several strategies for cancer screening in this patient population have been proposed. The development of these screening approaches has been hampered by the fact that there are no recommendations for endometrial cancer screening in the general population, unlike colonoscopy for colorectal cancer. Prospective studies comparing the outcome of those participating in colonoscopic surveillance with that of nonparticipants have demonstrated a reduction of CRC incidence by approximately 60 % and improved overall and CRC-related survival [104]. Current consensus guidelines recommend annual endometrial biopsy starting at age 30–35 years or 5–10 years prior to the earliest diagnosis of EC in the family, although the National Comprehensive Cancer Network does not recommend any specific screening for EC [105–107]. These guidelines are based largely on expert opinion as there are few prospective studies available to guide screening in this patient population.

Pro

Transvaginal ultrasound was the first modality utilized to help detect EC in women with LS, although it is now used mainly for ovarian cancer screening. Ultrasound is an attractive method for screening as it is noninvasive and relatively low cost. Unfortunately, ultrasound is unreliable in premenopausal women, who make up a large proportion of the patient population who are undergoing screening [108]. Not surprisingly, several studies have shown that ultrasound-based screening is

ineffective in identifying endometrial cancer in the Lynch population [109–112]. Dove-Edwin et al. found 2 endometrial cancers in 269 women who underwent annual transvaginal ultrasound. Neither of these cancers were diagnosed by screening and both presented with abnormal bleeding, were diagnosed at early stage, and were eventually found to be cured of their disease [111].

As transvaginal ultrasound alone is not a reliable method of screening, annual endometrial biopsy has been proposed as an alternative screening method. Previous studies have shown that endometrial biopsy has a high detection rate for hyperplasia and cancer in both premenopausal and postmenopausal women with a detection rate of 91 and 99 %, respectively [113]. Renkonen-Sinisalo et al. reported 11 cases of endometrial cancer found on screening in 175 women with known LS. Eight cases of cancer and 1 case of complex hyperplasia were detected on biopsy and an additional 14 cases of hyperplasia were also identified. While these cancers were detected during screening, there was no significant difference between stage at diagnosis and overall survival in patients undergoing screening matched with controls [110], although there was a trend toward improved overall survival in the screening group.

While the addition of endometrial biopsy may increase the detection rate of cancers in LS, a biopsy is an invasive procedure that causes discomfort for the patient. This could lead to decreased patient compliance when compared to noninvasive procedures, such as ultrasound. A recent prospective study showed that combined screening, with endometrial biopsy performed at the time of colonoscopy, decreases pain associated with the biopsy and increases patient satisfaction [107]. New strategies such as this may increase patient compliance and allow for a more thorough examination of annual endometrial biopsy as a screening method.

Annual endometrial biopsy is a safe, readily available procedure that has shown an improvement over transvaginal ultrasound for the detection of endometrial cancer in LS. While prophylactic hysterectomy and bilateral salpingo-oophorectomy have been shown to essentially eliminate the risk for endometrial and ovarian cancer in LS [114], many women who are diagnosed with LS have not completed childbearing and may not be willing to undergo hysterectomy. As such, annual endometrial biopsy is the best current option for endometrial cancer screening in patients who desire childbearing or decline prophylactic surgery. Further studies are needed to evaluate the impact of annual endometrial biopsy on stage at diagnosis and overall survival in women with a known diagnosis of LS.

Con

EC surveillance is less well established than that for colon cancer in LS families. Because many ECs can be diagnosed at early stages on the basis of symptoms, the efficacy of biopsy surveillance for cancer of the endometrium is unknown. Studies on the effectiveness of transvaginal ultrasound (TVUS) examination and endometrial biopsy (EMB) have had conflicting results.

In addition to the Renkonen study discussed above, a Finnish cohort of 103 LS women at risk for EC studied the long-term effectiveness of endometrial biopsy and TVUS performed every 2–3 years [115]. This is the largest study of healthy mutation carriers observed regularly over a long period. This surveillance of 11.5 years resulted in the diagnosis of 19 EC cancers. Gynecologic surveillance seemed adequate within the study period because most ECs were early stage and none of the EC patients died. However, the authors state that the effect of surveillance for EC is difficult to prove because the outcome of EC is favorable also in symptomatic patients and it could not be certain that the screening improved detection, because endometrial cancer often presents with symptoms at an early stage.

In the most recent study on this topic, on 41 LS women attending a clinic for EC screening, 69 office hysteroscopy-guided endometrial biopsies (OHES) were performed [116]. Four women were detected to have EC/atypical endometrial hyperplasia on biopsy. No interval cancers occurred over a median follow-up of 22 months. The authors conclude that OHES-based surveillance strategy has good performance characteristics for detecting early-stage EC in LS, but that definitive data would require larger multicentered studies. It is unknown if screening improved prognosis of these women in the long run and if the outcome of these women would have been different had they been diagnosed when symptomatic.

We conclude that until there are more data on this question, screening LS women for EC can be performed; however, these mutation carriers must be informed that this surveillance has not been proven to change their overall prognosis.

Concluding Comments

- BRCA testing for all high-grade serous ovarian cancer patients should be considered given the currently understood treatment implications.
- Large-scale prospective studies are needed to evaluate optimal screening strategies in patients with *BRCA* germline mutations.
- Triage methods of clinical criteria and molecular testing need to be rigorously evaluated to help formulate a cost-effective strategy with the highest clinical yield in the identification of Lynch syndrome in endometrial cancer patients.
- Prospective studies involving Lynch syndrome individuals are needed to evaluate the impact of annual endometrial biopsy on cancer diagnosis and subsequent survival.

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Trial Design: Should Randomized Phase III Trials in Gynecological Cancers Be Abandoned?

25

Mark F. Brady and Val Gebski

Summary Points

- The increasing use of molecular targeted therapy in the treatment of gynecological malignancies has raised many challenges – in study design, study conduct, and interpretation. For instance, should study designs require prospective biomarker testing or should the tests be performed after treatment allocation?
- Therapies shown to be effective in a particular subgroup, the biomarker positive population, have subsequently been shown to have potential benefit in the biomarker-negative population.
- Can many small phase II randomized studies using individualized therapies adequately substitute for larger phase III trials examining a fewer questions in a larger population of patients?

Introduction

Over the past 60 years, randomized phase III studies have evolved in sophistication and complexity. The rising cost of conducting a phase III trial for regulatory drug approval has also risen significantly [1]. At the same time, this study design has become increasingly idolized, and as a standard for clinical investigations, it has been declared "golden." Few investigators dare to speak against this idol lest they be smote. There is at least one rebellious soul, who contends that the randomized clinical trial is part of an archaic drug development system and foresees a time when this type of trial will be replaced by a more progressive "e-trial" design [2]. E-trials would permit patients to select any agent that has passed phase I testing. Then capitalizing on the same technologies that have been developed for e-businesses, like Amazon.com and Google.com, large databases track each patient's history as well as outcomes and would be used to guide the selection of treatments for future patients.

While we will not attempt to defend the e-trial concept in this chapter, we will attempt to unveil some of the shortcomings of randomized phase III trials. Firstly, the strengths and weaknesses of randomized and nonrandomized studies will be compared in order to determine whether nonrandomized trials can replace randomized trials. That section, however, can be considered a controversy within a controversy, because a relatively new methodological approach to analyzing nonrandomized studies will be presented, which is itself controversial. Secondly, the importance of phase IIa and IIb trials as a mechanism for eliminating unpromising phase III trials and guiding the development of phase III trials for promising agents will be presented. That section will distinguish the roles for randomized phase II versus phase III studies. The final section of this chapter assesses the role of randomized phase III trials in a world moving toward individualized medicine.

Should Nonrandomized Studies Replace Randomized Phase III Studies?

A well-known but often neglected shortcoming of randomized phase III trials stems from their unproven generalizability [3]. The first purpose of a study's eligibility criteria is to define the target population [4]. The results of the study are intended to apply to this population of patients. For instance, a study may target the enrollment of those patients who were diagnosed with ovarian cancer but progressed within

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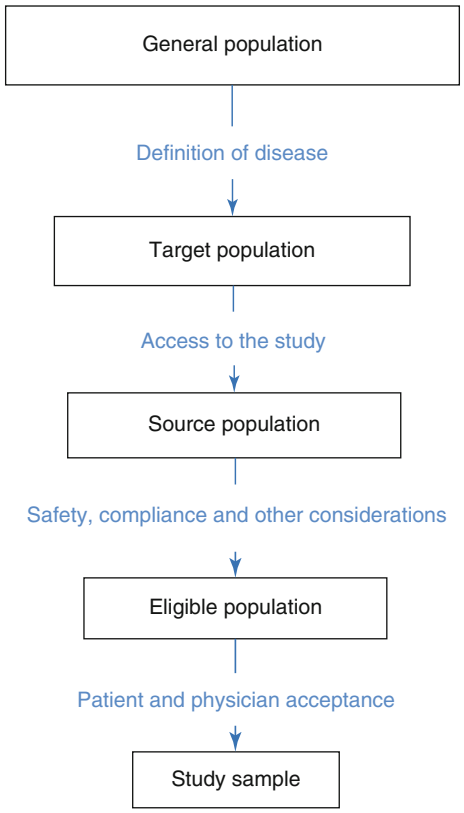

Fig. 25.1 Factors that determine the characteristics of the study sample

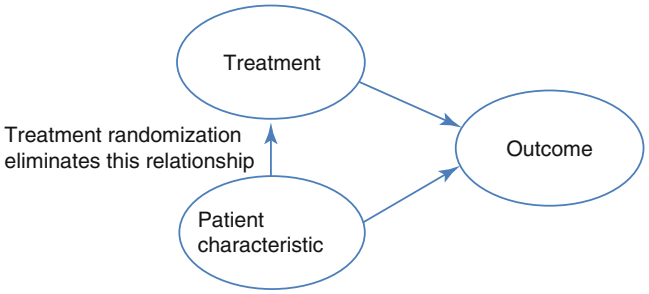

Fig. 25.2 Schematic representation of patient characteristics confounding treatment effects

6 months of completing their first line of chemotherapy. If that study results indicate that a new agent is safe and effective, then the new agent would become incorporated into the management of the future patients in this target population. However, not every patient in the target population would have had equal access to the study that identified the new agent. Patient referral patterns in the community often determine the type of patients who are ultimately enrolled onto a study. Patients with complicating disease factors may be more likely to be referred to large academic based centers, and wealthier patients may be referred more often to private clinics. If large academic centers are more likely to enroll patients into research studies, then it is unlikely that the patients in the source population are representative of those in the target population (see Fig. 25.1). Moreover, studies frequently include eligibility criteria that are intended to preclude patients who have difficulty complying with the study requirements or may have a significant risk of experiencing adverse treatment effects. For example, a study which requires that eligible patients have normal renal function not only directly eliminates this type of patient but also may indirectly limit access to disproportionately fewer older patients. Finally, a physician's attitude about the study treatment and the patient's ability to comprehend [5] the study can skew the type of patients who are enrolled on a study to differ from those in the target population. Generalizability, also called external validity, refers to the degree to which the trial results are applicable to the intended target population. The generalizability of a study's result depends on whether the patients enrolled onto a study are representative of the patients in the target population. The restrictions imposed on enrollment to a randomized trial, or any prospective study, that go beyond defining the target population threaten its generalizability. Some intrepid investigators have demonstrated the poor generalizability for particular randomized studies [6].

The proponents for randomized studies often point to the selection bias that is introduced when the study treatments are not randomly allocated. Figure 25.2 provides a simplified schematic representation of the causal relationship among the quantities that are measured in a standard clinical study. The primary objective of a phase III clinical study, regardless of whether the treatments are randomized, is to assess the causal relationship between a treatment and a clinical outcome. This is represented by the arrow connecting patient's treatment and her outcome in Fig. 25.2. Complicating matters, each patient has prognostic characteristics, such as disease stage, tumor grade, performance status, and age which are also associated with her outcome. Confounding is the distortion or the bias that is introduced into measuring the treatment's effect on outcome that is due to the association that a patient's pretreatment prognostic factors have on both the treatment selection and the patient's eventual outcome. For instance, many clinicians will only recommend intraperitoneal (IP) treatments to ovarian cancer patients with either no or only small residual disease following their staging surgery. Moreover, due to the potential for treatment-related complications, this treatment approach is used less often among elderly patients. It would therefore not be surprising for an investigator to find that those ovarian cancer patients in her practice who received an IP regimen tended to survive longer than those treated with conventional intravenous treatments. How much can be attributed to the treatment's effect and how much can be attributed to other factors? An unadjusted comparison of these treatments is

confounded with the effects that the patients' age and the extent of disease have on overall survival. A fair comparison needs to account for the presence of these confounding factors. One approach to dealing with confounding in the study design is to randomly allocate the treatments. This approach effectively eliminates the association between the treatment selection and the patient's pretreatment characteristics (see Fig. 25.2), because, on average, each patient has the same chance of receiving each of the study regimens regardless of her disease characteristics. Therefore, the estimated treatment effects are based on comparing groups of patients that have similar proportions of both known and unknown prognostic factors. Provided the follow-up of all the patients in the study is similar, except for the study treatment, the differences in the mean outcomes between the treatment groups can reasonably be attributed to either the study treatments or random error. In this case, treatment randomization provides the theoretical underpinning for interpreting the p-value from an appropriate statistical test.

In summary, randomized clinical trials control the bias that is due to confounding between pretreatment prognostic factors and treatment selection. However, typically the cost of controlling this source of bias is indeterminable generalizability, since randomized trials seldom, if ever, randomly select patients from the target population. On the other hand, one could imagine selecting a representative cohort of patients from a population-based registry, without randomizing treatments and analyzing these patients based on the treatments that they actually received. The advantage of this sort of study is generalizability, but the cost is potential confounding of the treatment effects with prognostic factors.

Propensity Scores

Are nonrandomized studies hopelessly muddled? In order to deal with confounding, Rosenbaum and Rubin proposed a coarse balancing function called the propensity score [7]. Rubin has provided the rationale for using propensity scores in observational studies to approximate randomized experiments [8], and D'Agostino described alternative approaches to analyzing studies using propensity scores when the study involves a nonrandomized control group [9, 10]. Propensity scores and how they can be incorporated into the analyses of observational data will be briefly presented here followed by an example. Finally, areas where propensity scores have been used to extend the interpretation of randomized phase III trials will be described.

In a prospective trial, treatment randomization can be used to balance the prognostic factors across the treatment groups. However, in the absence of randomization, a balancing function may be incorporated into the analysis. With a suitable balancing function, the conditional distribution of the patients' characteristics, given the value of their balancing function, will be the same for the treated and untreated individuals. In this way, balancing functions are used to decrease the bias in observational studies. Propensity scores are used as a "coarse" balancing function [7].

The propensity score is the likelihood that a patient will receive a specific treatment given her characteristics and the characteristics of her disease. For a randomized trial, the propensity score is determined by the design (i.e., the treatment allocation ratio); for an observational study, it is unknown, but it may be possible to estimate it. When the patients' confounders are multivariate normal, a discriminant function can provide an estimate of the propensity scores; otherwise, a logistic or probit model is often used. The estimated propensity scores are then used as matching, stratification, or regression variables in the analyses of the treatment's effect on the outcome. In order to appreciate the key assumptions that underlie the use of propensity scores as a balancing function, it is useful to think in terms of the counterfactual model for causation. Imagine it were possible to treat an individual with the study intervention and then measure her response. Then roll back time so that the subject is in the exact same initial state as the first experiment. Repeat this entire one-patient experiment, this time without applying the study intervention. If this were possible, each individual would provide two outcome measurements, one for each therapeutic approach, and the difference in her responses could be attributed to the effect of the intervention. In reality, however, either the study intervention is applied or not, and only that corresponding response can be measured. The patient's counterfactual response is unobserved, and therefore, it is unknown. Propensity score analysis attempts to estimate a patient's counterfactual response from the observed responses of the other patients. There are important assumptions required in order to use the propensity score procedure to estimate the treatment effects from this type of data: (1) the outcomes (both the measured and counterfactual outcomes) and the treatment selection processes must be conditionally independent given the values of the measured covariates. This means that there can be no unmeasured confounders. (2) The relationship between exposure and the covariates must be correctly specified. (3) Every person in the study cohort must be at risk, but not predisposed, of being exposed or left unexposed to the study intervention. For instance, an observational study that intends to measure the response to doxorubicin for the treatment of endometrial cancer would not include those patients with a history of significant heart disease, since doxorubicin is medically contraindicated in these patients and they are considered not "at risk" of receiving this treatment. (4) The responses for each individual must be independent. In other words, the response of one individual does not influence the response of another.

Table 25.1 Pretreatment patient characteristics by ESA usage within the first 5 months of starting chemotherapy (the landmark period)

	Unadjusted				Adjusted[c]	
Pretreatment characteristic	No ESA[a]	ESA	Rel. odds	*P*-value[b]	Rel. odds	*P*-value
	N=1,445	*N*=419				
Performance score				<0.001		0.948
0	52 %	41 %	Reference		Reference	
1	41 %	49 %	1.51		1.01	
2	6 %	10 %	2.19		1.08	
Stage/residual size of tumor				<0.001		0.949
III, less than 1 cm	37 %	23 %	Reference		Reference	
III, at least 1 cm	39 %	45 %	1.91		0.949	
IV, any size residual	24 %	33 %	2.27		0.974	
Hemoglobin (gm/dl)				<0.001		0.879
<11.0	24 %	36 %	Reference		Reference	
11.0–12.4	46 %	46 %	0.667		0.995	
≥12.5	30 %	18 %	0.404		0.918	
Age (years)				0.16		0.979
<60	51 %	46 %	Reference		Reference	
60–64	17 %	19 %	1.21		0.974	
≥65	31 %	35 %	1.24		0.967	

[a]ESA exposure is based on whether the individual received an ESA during their landmark period. Nine patients received an ESA after their landmark period and classified in this table as unexposed
[b]Relative odds and *p*-values are from univariate logistic regression which modeled the log relative odds of starting an ESA within 5 months of beginning chemotherapy
[c]Relative odds and *p*-values are from the same logistic model, but stratified by the quintiles of the propensity score

Illustrated Example

Erythropoietin-stimulating agents (ESAs) are occasionally used during chemotherapy, since they have been shown to increase hemoglobin levels, reduce the need for blood transfusions, and improve quality of life [11]. A recent multi-institutional retrospective review of women treated for ovarian cancer, however, suggested that ESAs increase the risk of death and disease progression [12]. In order to demonstrate an analysis with propensity scores here, data from GOG-0218 [13] will be used to assess ESA usage during first-line chemotherapy and its impact on the risk of death. In this study the first-line chemotherapy was randomly determined, but erythropoietin usage followed the treating physician's medical judgment with some protocol guidelines. An analysis of these data involving a time-dependent proportional hazards model has been published elsewhere [14]. An analysis using propensity scores is presented here as an example. This analysis is intended as an illustrated example and not a thorough consideration of the risks and benefits of ESAs.

GOG-0218 was a randomized, placebo-controlled phase III study involving 1,873 women with newly diagnosed ovarian, fallopian, or primary peritoneal cancer. This trial evaluated the addition of bevacizumab to standard first-line carboplatin and paclitaxel, as well as a single-agent maintenance treatment. The subjects were enrolled within 12 weeks of their initial staging surgery, but before starting any chemotherapy. The enrollees were to receive 21 cycles of bevacizumab or placebo unless disease progression or toxicity precluded further treatment. A case report form (CRF) that recorded the administration of study agents as well as ESA administration was completed after each cycle of study treatment. A landmark period was defined for each patient as the first 5 months from starting chemotherapy. Any patient who initiated an ESA during this landmark period was classified as exposed. There were nine subjects who started ESAs *after* their landmark period, and therefore classified as unexposed in this summary. The following analysis focuses on determining whether ESAs increase the death rate following the landmark period.

Table 25.1 summarizes some of the pretreatment characteristics of those individuals who were or were not exposed to ESAs during their landmark period. The columns in the section of the table, which is labeled "unadjusted," report the observed percentage of patients with each of the pretreatment disease characteristics and ESA usage. The univariate relative odds of exposure are also provided. These data show that those individuals who received ESAs during the landmark period had significantly poorer initial performance status, more advanced stage of disease, and lower initial hemoglobin levels ($p<0.001$) prior to starting any chemotherapy. Those who received an ESA were also slightly older, although this difference was not statistically significant. It is important to point out here that the imbalance of a prognostic factor does not need to be deemed statistically

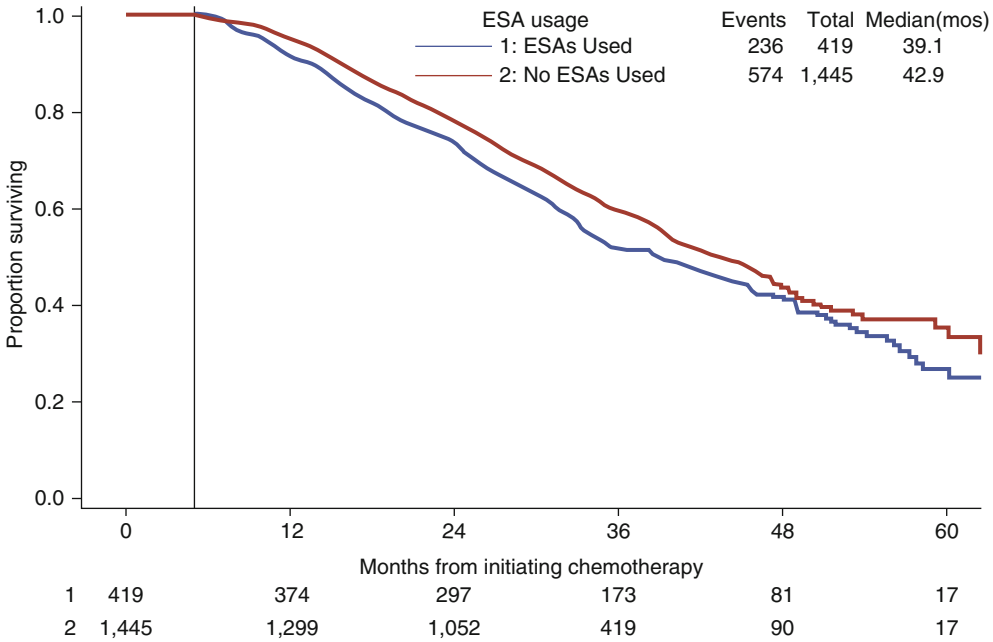

Fig. 25.3 Unadjusted probability of survival following the landmark period by erythropoietin usage

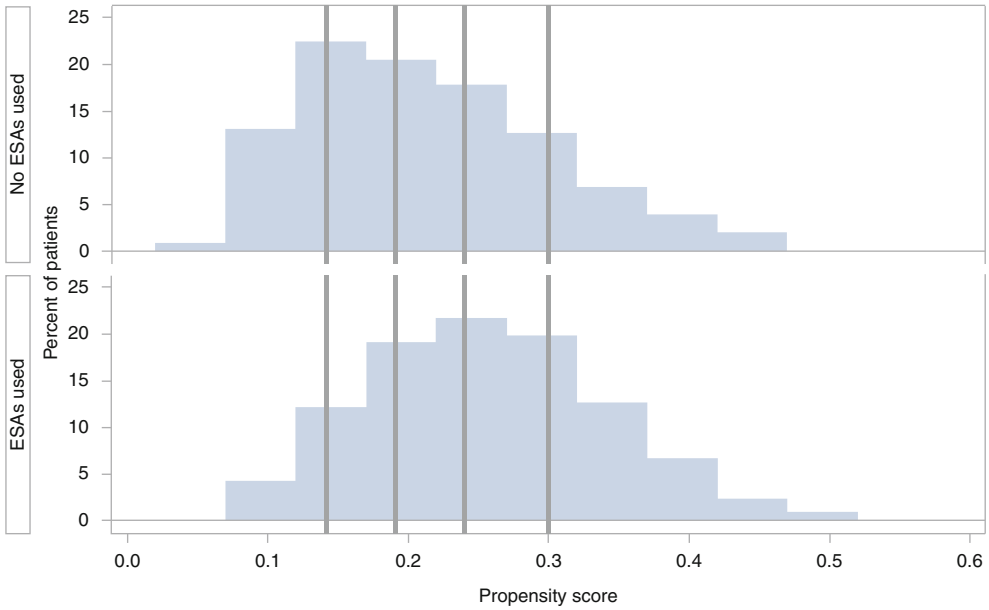

Fig. 25.4 Distribution of propensity scores by ESA usage

significant in order to confound the final analysis. Since these factors are generally regarded as prognostic for overall survival, any crude comparison of ESA exposure with regard to overall survival will therefore be biased against the group exposed to an ESA. This is apparent in Fig. 25.3. These Kaplan-Meier curves indicate that the crude death rate is higher among those patients who received ESAs during their landmark period. A proportional hazards model estimates that the unadjusted (not accounting for the confounding) death rate is 19 % higher (hazard ratio: 1.19; 95 % confidence interval: 1.02–1.38; $p=0.024$) among those treated with ESAs.

In order to adjust for the bias due to confounding, a multivariate logistic model that included the pretreatment factors in Table 25.1 was used to estimate the probability of exposure to an ESA during the landmark period (propensity score). The distributions of the propensity scores for the exposed and unexposed individuals are plotted in Fig. 25.4. For the purposes of this analysis, the patients were then grouped into strata determined by the quintiles of the estimated propensity scores. That is, five mutually exclusive strata were constructed, each containing 20 % of the patients from the entire sample. The vertical lines in Fig. 25.4 demarcate the propensity scores used to construct the strata.

Table 25.2 Characteristics of patients by ESA exposure and stratum-level determined by propensity score

	Stratum 1			Stratum 2			Stratum 3			Stratum 4			Stratum 5		
	No ESA	ESA	Δ	No ESA	ESA	Δ	No ESA	ESA	Δ	No ESA	ESA	Δ	No ESA	ESA	Δ
Stage and residual size[a]															
Stage III, <1 cm	89 %	80 %	9 %	50 %	52 %	−2 %	22 %	26 %	−4 %	9 %	7 %	2 %	1 %	3 %	−3 %
Stage III, ≥1 cm	9 %	11 %	−2 %	37 %	36 %	1 %	54 %	51 %	3 %	52 %	57 %	−5 %	49 %	45 %	4 %
Stage IV	3 %	9 %	−6 %	13 %	12 %	1 %	24 %	23 %	1 %	39 %	36 %	3 %	51 %	52 %	−1 %
Performance status[a]															
PS 0	81 %	77 %	4 %	61 %	58 %	3 %	54 %	61 %	−7 %	39 %	35 %	4 %	13 %	14 %	−1 %
PS 1	19 %	23 %	−4 %	39 %	42 %	−3 %	45 %	39 %	7 %	61 %	65 %	−4 %	87 %	86 %	1 %
Age at enrollment (years)															
Mean age	55.9	58.0	−2.1	57.7	59.7	−2.0	59.5	59.4	0.1	61.5	61.6	−0.1	63.8	62.3	1.5
Initial hemoglobin (mg/dl)															
Mean HGB	12.7	12.9	−0.2	12.2	12.2	0.0	11.8	11.6	0.2	11.3	11.4	−0.1	10.4	10.4	0.1
Total patients	337	35		309	64		286	87		274	99		239	134	

Δ is the difference in percentage between those who did and did not receive ESAs within the stratum
[a]Percent of patients within the stratum and ESA usage

Provided the previously mentioned assumptions are satisfied, the patients within each stratum will tend to have similar distributions of those prognostic factors that were used to estimate the propensity scores. Specifically, Table 25.2 displays the distributions of the pretreatment characteristics for each treatment group within each of the five strata. There are clear differences in the distribution of these characteristics across the strata; however, the differences between the treatment groups within any specific stratum are not large. In fact, the differences between treatment groups are on par with what would be expected if randomization had been used within the strata to assign ESA treatment. Clearly, the treatment allocation ratio is not 1:1, nor is the allocation ratio the same within each stratum. Nevertheless, factors are reasonably balanced across the treatment groups within each stratum, except for stratum 1. Closer examination of Table 25.2 suggests that there may be some residual confounding present in stratum 1. Those patients who did not receive ESAs were slightly more likely to have stage III disease with small residual disease, have normal performance score, and are younger. Return to the histogram in Fig. 25.4. Note that there are some patients with a very low propensity score in strata 1, who have no counterpart among those who were exposed. Therefore, the inclusion of these patients in the subsequent analysis would require some degree of extrapolation, because there are no real patients in the ESA-treated group with whom they can be compared. If this is of significant concern, then the analyst could opt to further stratify the individuals in stratum 1. Indeed, if one more cut point was set anywhere lower than the lowest propensity score of the exposed group, then this would effectively eliminate the patients with the most extreme propensity scores from the calculation of treatment group differences when a stratified analysis is performed. One of the advantages of propensity score analyses is that it permits a direct assessment of how well confounding is being addressed when the data are presented as in Table 25.2 and Fig. 25.4. For the purpose of this illustrated example, the subjects in stratum 1 will not be further stratified.

The columns labeled "adjusted" in Table 25.1 provide the weighted average (over the propensity score strata) odds of exposure for each patient characteristic. These values are near 1.0, and there is no significant heterogeneity in odds among propensity score strata (data not shown); therefore, these factors appear fairly well balanced across the treatment groups within the strata. Once the balance of covariates has been adequately addressed, a second stage of analysis can begin. It is important to note that up until this point, the analysis has not even considered the outcome for this analysis, survival.

In order to address the effect of ESAs on overall survival, a proportional hazards model was selected for the second stage of the analysis. A proportional hazards model, stratified by propensity score quintiles, was used to estimate the death rate for those individuals who were exposed to ESA relative to those who were not exposed. This analysis indicates that the death rate is only 3 % higher (hazard ratio: 1.03; 95 % confidence interval: 0.877–1.20; $p=0.736$) among those

exposed to ESAs. A non-stratified proportional hazards model that included the propensity score as a continuous covariate also provides a similar result (hazard ratio: 1.03; 95 % confidence interval: 0.885–1.21). A test for treatment-propensity score interaction is not statistically significant ($p = 0.484$). Unlike the crude analysis, the adjusted analyses indicate that there is no appreciable increase in the death rate due to ESA usage during first-line chemotherapy for the treatment of advanced ovarian cancer and that earlier reports from observational studies may have inadequately addressed bias due to confounding.

Why Use Propensity Scores?

It is reasonable to ask why someone would use propensity scores to control confounding in nonrandomized studies, rather than the usual multivariate regression which is the approach that is used in most epidemiologic studies. Rubin has argued that it is preferable for scientific studies to be conducted in two separate and distinct phases: design and analysis [8]. Consideration for those procedures that will control confounding should occur during a design phase where the confounders are examined without knowledge of the study outcomes. This occurs naturally with the propensity score approach, since only the probability of exposure is evaluated during the design phase and the outcomes of each individual can and should remain unknown during this phase of the analysis. This approach is similar to that implemented in randomized clinical trials. Indeed, most reviewers would be naturally wary of the interpretation from a randomized trial in which the analysis plan was not pre-specified, but developed after the study team had access to the outcome data. Why should observations studies be held to a lesser standard?

Stratified propensity score analyses permit the analyst to evaluate the degree of imbalances in a natural way. Summaries like those in Table 25.2 permit a visual presentation of the comparability of the groups that are being contrasted. This feature is not available when a multivariate regression is simply used to directly model the study outcome in observational studies. The linear relationships used in regression analyses are often simply and tacitly presumed.

It may be reasonable to consider study designs that match exposed and unexposed individuals based on the observed values of their covariates in order to control confounding. However, as the number of covariates increases, so does the complexity of matching. Moreover, when there are several covariates to be matched, it becomes increasingly difficult to identify exact matches for each individual. Eliminating cases from the analysis due to an inability of identify a matching control, or vice versa, is undesirable since this reduces the precision of the study. D'Agostino has suggested alternative approaches to near matching based on propensity scores [9].

The results from propensity score analyses have been compared to standard multivariate regression [15, 16]. It appears that propensity score-based procedures yield similar results when compared to conventional regression methods. However, the conclusions from stratified propensity score-based methods tend to be slightly conservative (i.e., larger p-values). Specifically, it has been observed that "propensity score stratification treats bias as paramount and variance as secondary" [17]. In other words, there appears to be a modest price to pay for using propensity scores to control confounding, and this price is a slightly larger variance.

At first it may seem counterintuitive to analyze the probability that each individual will be exposed rather than analyzing her actual exposure status. The propensity scores are simply a mechanism for adjusting the treatment comparisons in order to control bias from confounding. It is similar to the randomized trial in that it attempts to address confounding during the design phase. However, it is not a panacea. Randomized trials can remove the bias due to unknown or unanticipated confounders. Regardless of the analytic approach, confounding biases from unknown factors cannot be definitively addressed in observational studies. The analyses of observational studies require a strong assumption that there are no unmeasured confounders and that the relationship between confounder and outcome is correctly modeled. A doubly robust estimation procedure has recently been proposed which extends the propensity score approach. This newer approach requires that either the propensity score model or the outcome regression model be correctly specified, but not necessarily both [18].

Using Propensity Scores to Extend the Analysis of Randomized Trials

The preceding section considers the effects of confounding due to the imbalances of pretreatment prognostic factors. Confounding can also occur during the study's follow-up period, even when the prognostic factors are initially balanced, as in a randomized treatment trial. Subjects may prematurely exit the study or stop their designated treatment before the endpoint is measured. If the mechanism that leads to missing outcome measurements is related to the subjects' overall prognosis and assigned treatment, then the treatment comparisons become confounded. For example, study participants may become unable to return to the clinic for follow-up assessments due to a deteriorating health status. If their deteriorating health status is a harbinger of the study outcome, like progression or death, and imbalances in the censoring patterns between treatment groups evolve, then the missing observations can introduce a bias into the treatment

comparisons. Also, if patients who were initially allocated to the experimental treatment opt to discontinue it or patients who were initially allocated to the reference treatment opt to start the experimental treatment, then this will bias the treatment comparisons. If the reasons for missing measurements are associated with the subjects' prognosis, then this is called informative censoring. If the informative censoring is differentially dependent on the study treatment, then the usual intention-to-treat approach to estimate the true treatment effect can become biased.

To address these sources of bias, an inverse probability of censoring weighted (IPCW) approach has been proposed [19]. In this case, each subject's conditional probability of continuing to take study treatment or continuing to be assessed given the value of her covariates is modeled. This approach is similar to the estimating the propensity score describe above. However, the IPCW procedure actually uses the reciprocal of the probability of continuing treatment to reweight the subjects in a regression analysis rather than to create strata. More importantly, as opposed to being a static probability that is estimated once for each subject, IPCW uses a cumulative probability function to estimate the probability at any given time during follow-up period that a subject will be receiving her study treatment and compliant with assessments for the study outcome. This approach is used to account for the confounding that can arise during the follow-up period due to subjects prematurely switching treatments or dropping out of the study. For example, BIG I-98 is a 4-arm randomized trial for which one objective was to compare letrozole to tamoxifen with regard to disease-free survival for the treatment of postmenopausal women diagnosed with hormone receptor-positive early invasive breast cancer [20]. There were 4,922 women randomly assigned to 5 years of adjuvant treatment with either letrozole or tamoxifen. Among the 2,459 women allocated to tamoxifen (the reference regimen), 629 (25 %) crossed over to letrozole (the experimental regimen) within 5 years of starting tamoxifen. The usual intention-to-treat analysis which does not account for treatment crossover indicated that letrozole reduced the relative DFS event rate 13 %. After accounting for the crossovers, the IPCW analysis estimates that the true effect of letrozole is to reduce the DFS event rate 18 %. As would be expected, those patients who were randomized to tamoxifen but crossed over to letrozole tended to bias the usual intention-to-treat analysis toward no difference.

Summary

In summary, the debate concerning whether more meaningful results can be obtained from randomized studies or observational studies forces us to recognize the strengths and weaknesses of each study type. A well-conducted randomized phase III study can demonstrate that a treatment is active. However, the true target population may be somewhat ill-defined because randomized studies do not ensure that the study sample is representative of the intended target population. Observational studies can be used for treatment comparisons when randomization is not a viable option. Provided the biases due to confounding can be properly managed, observational studies can also provide significant insights into the effect of treatments in those subgroups of patients who are otherwise underrepresented in randomized trials [6, 21]. Moreover, extending the techniques to adjust for confounding in observational studies to account for noncompliance in randomized studies can improve our understanding of treatment effects.

Are More Randomized Phase II and Fewer Randomized Phase III Studies Needed?

Background

In the age of evidence-based medicine, clinical practice adapted from the emerging evidence of the results of clinical trials is now a key component driving changes in therapy. Historically, results of clinical trials took many years to change practice, which is well illustrated by in the use of antibiotic prophylaxis in colon cancer surgery [22] shown in Fig. 25.5.

The evidence of the benefit of antibiotic prophylaxis in the prevention of perioperative infection and reduction of operative mortality was available as early as 1977, but due to the reluctance to adopt the intervention into practice, trials evaluating the benefit of antibiotics were still being conducted some 10 years later.

Fortunately, in gynecological malignancies, uptake of evidence-based interventions into clinical practice is more rapid. For instance, the combination of carboplatin and paclitaxel quickly replaced platinum for the treatment of women with platinum-sensitive relapsed ovarian cancer following the ICON 4/AGO trial [23]. This evidence was sufficient to change practice as has more recently, the substitution of pegylated liposomal doxorubicin for paclitaxel for the treatment of women with relapsed ovarian cancer [24]. A common thread of all these studies is their sample sizes, 802 for the ICON4/AGO trial and 976 in the CALYPSO trial. Such large studies require substantial budgets, multinational collaboration, and multicenter involvement.

Randomized Phase II (IIa and IIb) Trials

With the emergence of new targeted therapies, the horizon is not as clear as one might hope. Targeted therapies have

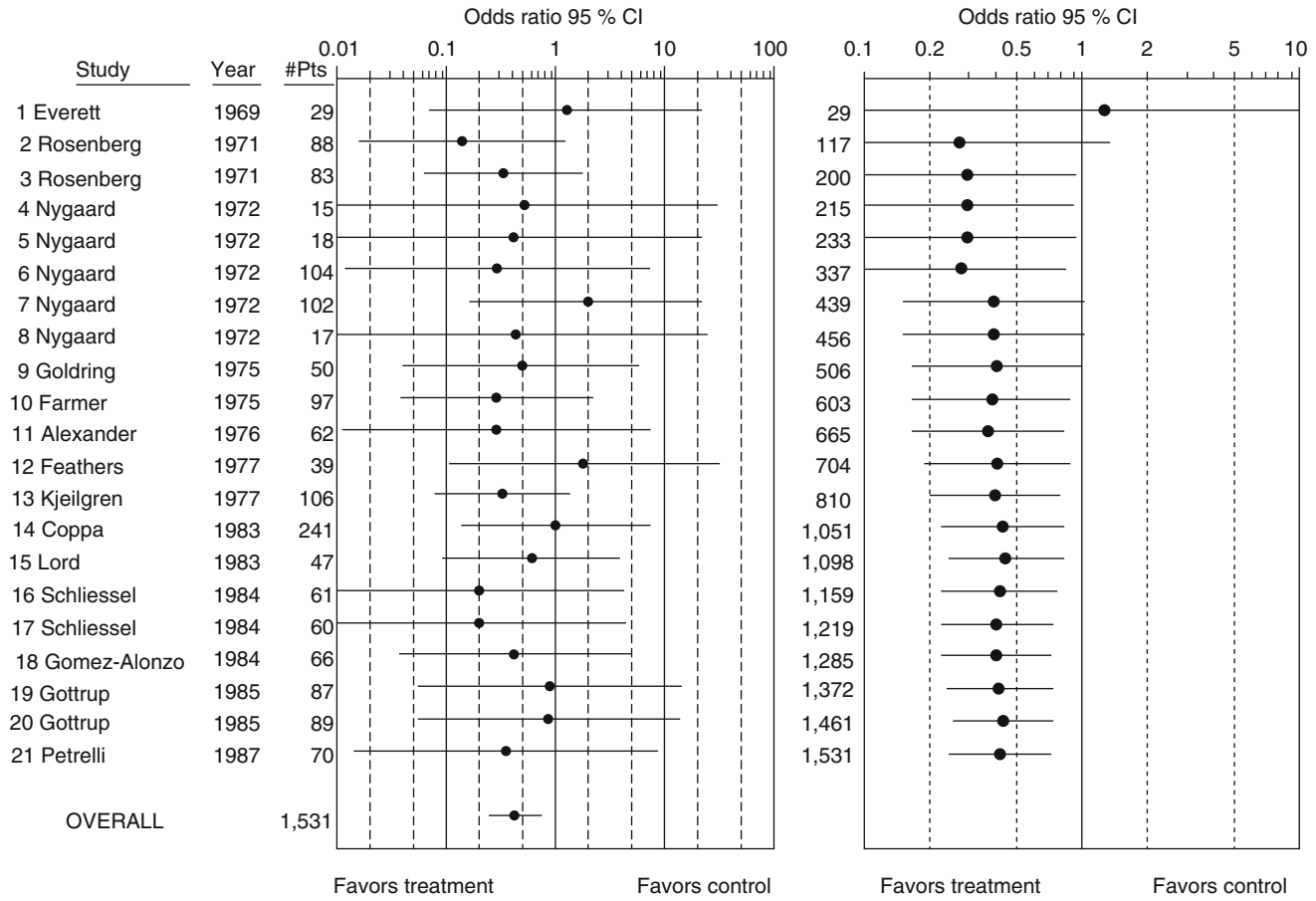

Fig. 25.5 Reduction of perioperative deaths by antibiotic prophylaxis for colorectal surgery. Studies were pooled by the Mantel-Haenszel method and cumulative meta-analysis is based on publication year (From Ref. [22])

shown a survival benefit in those patients who have HER2+ breast cancer tumors in the HERA-2 trial [25] and K-Ras wild-type patients with colorectal cancers in the CO17 trial [26]. The benefits of targeted therapies have been mixed; trastuzumab demonstrating a survival benefit in HER2+ patients in breast [27] and gastric cancers [28], bevacizumab not showing any long-term benefit in the treatment of early colorectal cancer [29], and only a modest progression-free survival benefit in ovarian cancer but no benefit in overall survival [30, 31]. These trials were also large with sample sizes of between 500 and 2,900 patients. So, the challenge is to develop designs which can detect the strength of signals much sooner and with a lower cost burden than traditional randomized phase III trials (RCTs).

Over the past two decades, the pilot or single-arm phase II study has evolved to attempt to address some of these challenges, driven in part by the need for rapid drug development and picking winners in a much smaller cohort. The phase II trial is the next step from a phase I, dose finding study (usually between 6 and 20 patients) and is the first step in developing evidence for a "proof of concept" of the therapy under investigation. Typical questions addressed in a phase IIa study would include:

- How consistent is the data with an x% success rate? (e.g., is the data consistent with a 35 % response rate?)
- How consistent is the data with a y% toxicity/morbidity rate? (e.g., is the surgical morbidity consistent with the current rate of 7 %?)
- Does treatment do what it is supposed to?
- How does treatment affect the physical, biological, and clinical aspects of the patient?

Data can be analyzed at key interim times (say after 10, 20, 30 patients have been accrued) and the results examined to decide whether to continue/abandon the study, modify the treatment, or enrich the patient population being recruited. This study design generally involves a single arm but sometimes randomization may be appropriate and is sometimes referred to as a *phase IIa* trial. Historically, single-arm phase IIa studies were fixed in their sample size, and interim analyses (planned and unplanned) were periodically performed without any formal strategy, and stopping rules were developed to guide decisions of futility [32]. Formal methods for sample size calculations in a randomized phase IIa studies

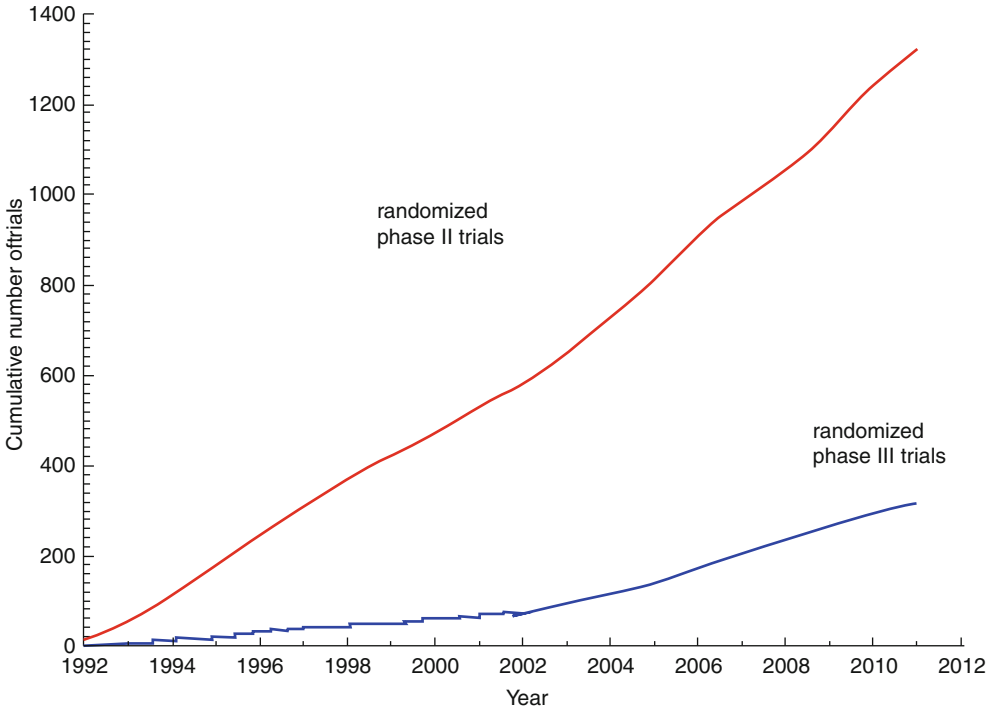

Fig. 25.6 Cumulative total of randomized phase II and phase III trials in gynecological oncology since 1992

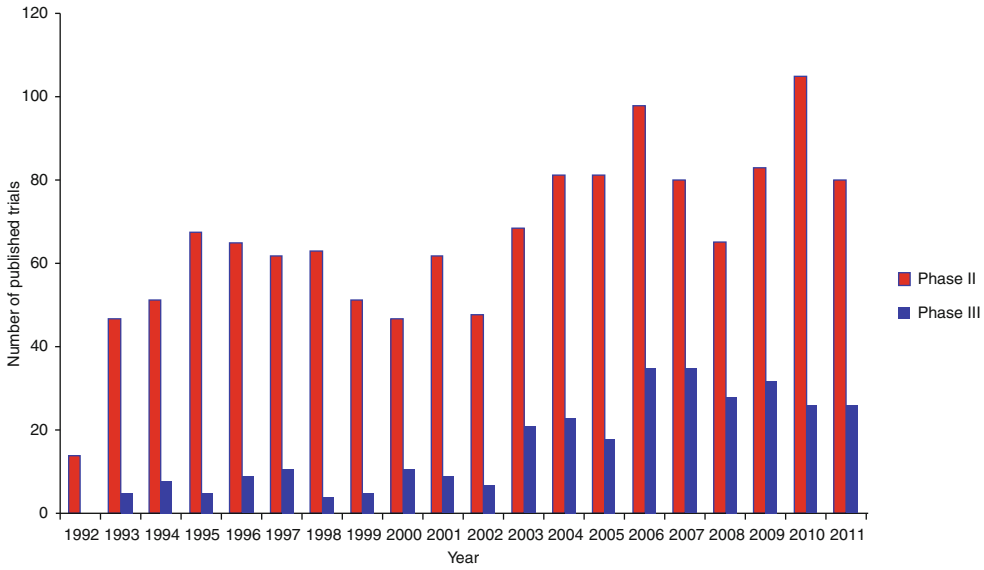

Fig. 25.7 Number of randomized phase II and phase III trials in gynecological oncology since 1992

were developed by several authors [33, 34], and the concept gained attention.

Figure 25.6 shows the cumulative number of randomized phase II trials and phase III trials in gynecological oncology over the past 20 years as referenced in PubMed. There has been an almost fourfold increase in the number of randomized phase II studies compared with the phase III RCTs.

The number of trials in each year is given in Fig. 25.7.

Given this emphasis in randomized phase II trials, it is instructive to examine the differences between the underlying assumptions and how they differ from the phase III RCTs.

As mentioned earlier, the main purpose of the phase II study is to determine whether the intervention has sufficient activity to warrant further investigation in a selected population (often those in whom conventional treatment has failed), and as such the rules governing the running of the study can be somewhat relaxed compared to the phase III counterpart. In single-arm pilot/phase II, the main sources of variability [33] include:

(a) *Selecting patients into the study* – which patients are selected to participate in the phase II trial can be variable and not necessarily representative of the broader population to which the intervention will be applied. These patients may comprise of a heterogeneous cohort of

high-/low-risk group for the event of interest, making extrapolation to the general population with the disease problematic.

(b) *Determining treatment activity* – response to therapy is generally assessed at the treating site and seldom centrally audited. Variability with regard to classifying response may arise between different investigators. This would especially be the case in patients with poor performance status where frequency of scans could be highly variable across sites.

(c) *Intra-observer variability in response assessment* – it is well known that response assessment can be susceptible to measurement error [35]. Tumor assessment by palpation, for example, can lead to large misclassification bias yielding an over-/underestimate of the potential efficacy of the new therapy.

(d) *Modification of therapy/dose and compliance with the protocol* – the heterogeneity of patient population enrolled in the phase II study will invariably result in dose modifications which depart from the schedule recommended in the protocol. This in turn can impact on outcome and lead to an over-/underestimate of therapy benefit.

(e) *Reporting procedures* – there can be a large degree of variability when reporting of response rates, toxicity profiles, and treatment delivery. There tends to be some inconsistency among authors on how or when to include patients, who were not entirely evaluable for response. This can lead to optimistic/pessimistic estimates of response rates which may not then be borne out in subsequent phase III trials.

(f) *Sample size* – as mentioned previously, the sample size is generally set in advance based on what is felt would be "adequate" (i.e., providing reasonable estimates of precision) without too much attention being given to excluding "uninteresting" levels of activity. Since the work of Simon [34], this has changed somewhat, and adaptive multistage procedures [36] are now mainstream in the design of phase II studies.

The role of randomization is to balance these potential biases among the treatment arms and therefore reduce the systematic differences between treatment groups [37, 38]. In this way, the randomized treatments are place on an equal footing. However, the goal of a randomized phase *II*a study is not to make direct comparisons between the treatment groups, since these studies are not designed for this purpose.

Why Treatment Comparisons in Randomized Phase IIa Trials Are Not Desirable

The main purpose of phase IIa trials is to determine whether an intervention has sufficient activity to warrant further investigation. These designs usually do not have sufficient statistical power (i.e., low probability of declaring the intervention worthy of further investigation when it is in fact active) when experimental regimens are compared to a standard regimen. This is primarily due to the small sample sizes but is also a function of the choice of endpoints (e.g., response rather than survival), length of follow-up, and the detailed treatment schedule protocol. Phase II studies often focus on surrogate endpoints – response in lieu of progression-free survival (PFS) or PFS at a specified time point (say at 3 months) in lieu of PFS or overall survival (OS). So why are comparisons in randomized phase IIa designs discouraged?

Suppose for example we wish to evaluate an antiangiogenic multi-targeted tyrosine kinase (TKI) inhibitor in platinum-resistant ovarian cancer; investigators might consider a response rate of 20 % as not being clinically useful to warrant further interest in the TKI. However, a response rate of 40 % would be clinically interesting and warrant further investigation. Using exact procedures, a sample size of 35 patients would have >80 % power with 95 % confidence to rule out a response rate of 20 % or lower and rule in a true rate of 40 % or higher. This implies that at the end of the trial, if the true response rate is 40 %, the odds are 4:1 that the 95 % confidence interval for the estimated response rate (from the study) would exclude 20 % and include 40 %. So, if we observed 16 responses in 45 patients, the 95 % confidence interval is [22 % to 51 %]. Based on this result, we would consider the TKI sufficiently active to justify further investigation, provided there were no untoward safety effects.

Now, if we use the previous sample size (35 patient) calculation for a phase IIa trial, but intend to compare the 35 patients treated with a reference regimen to 35 patients treated with the TKI, the statistical power to detect a 20 % improvement drops to 56 % (not 80 %). The two-arm comparative phase IIb trial would require 64 patients in each treatment group, in order to retain 80 % power. The efficiency of the IIa trial design arises from regarding the response rate in the reference arm (20 % in this case) as a fixed quantity. That is, it is assumed to be known with certainty. Occasionally, the probability of response to an appropriate reference regimen can be obtained from a large historical database or the literature. In this case, a phase IIa trial design may be reasonable. However, in the current era of targeted treatments, the probability of responding to a reference regimen, for a population that is identified by a specific biomarker, is often unknown. This has contributed to the increase use of randomized phase IIb trials over the past several years. The advantage of randomization is both to reduce biases and provide a contemporary estimate of the benefit which could be seen in the standard therapy arm.

Phase IIb Trials

The above discussion relates to designs with the focus being on identifying the activity of therapy, commonly using

response (tumor shrinkage). A further development of the phase II concept is the randomized phase IIb design [39, 40] where the designs align themselves to the study of molecular targeted therapies which impact on PFS and OS but not necessarily on response [41]. In these designs, the inclusion of a reference group and treatment randomization is often paramount.

Phase IIb studies are specifically designed to make direct comparisons between a reference group and group receiving the experimental regimen(s). Thus, in a phase IIb trial, a goal might be to identify new treatments that provide a minimum of 20 % absolute increase in 6-month PFS from say 35–55 %. Unlike phase IIa studies, the phase IIb study design is specifically designed to account for the uncertainty of the response rate in the reference group. Whether a phase IIa study is randomized or not, the study usually does not include a reference arm. Instead, these studies are designed to compare the response rate of the experimental arm(s) to a fixed reference value. This reference value is assumed to be known with certainty (i.e., without error). Phase IIb trials, on the other hand, often include either a historical or concurrent reference group in order to provide an estimate of the reference response rate. This estimated value is associated with some degree of uncertainty. In this way, the phase IIb design accounts for the uncertainty in the reference response rate, which leads to the per-arm sample sizes for phase IIb trials being generally larger than phase IIa trials.

Randomized Phase III Designs

The rules pertaining to phase III trials are more rigorous, giving little flexibility to deviate from pre-stated hypotheses, procedures, endpoints, and proposed analyses and treatment comparisons, subgroups, and statistical methods. Guidelines to the content and structure of reporting the results of phase III studies have been extensively promoted through the CONSORT statement [42, 43]. The methodological and statistical underpinning for randomized phase III trials include precise statements/definitions of:

(a) Primary endpoint(s) and how they relate to patient outcomes – an endpoint could be, for example, the *proportion* of patients who experience >15 % leg swelling following surgery for vulva cancer, while the outcome would be whether an *individual* patient experiences leg swelling >15 %.
(b) Study design(s) to best address the hypothesis being investigated – this could involve treatment comparisons to evaluate superiority/efficacy, equivalence, or non-inferiority of the experimental intervention. The design could involve investigating multiple interventions either as a factorial design [44], a multi-arm study [45, 46] with or without a run-in phase [47].
(c) Principles of statistical analysis – treatment comparisons could be based on intention-to-treat and/or per-protocol treatment (and the definitions of the patient populations on which these analyses will be based). Comparisons based on per-protocol treatment received are typically used for safety and toxicity considerations. An outline of statistical methods including procedures for statistically accounting for missing outcomes and strategies to be employed if statistical assumptions are not satisfied (e.g., the proportional hazards assumption is violated in outcomes which are time to event) should be provided. Pre-specified definitions of subgroups and potential variables to be used in prognostic modelling and subgroup analyses are appropriate.
(d) Target sample size to meet statistical criteria of power (generally 80 %) and confidence (generally 95 %) as well as any adjustment for compliance (treatment drop-in or drop-out) and lost to follow-up. Sample size calculations should be reproducible with a clear outline of the value of the statistical parameters and underlying assumption on which the calculations were based.
(e) Precise outline of interim analysis plan including potential stopping boundaries, frequency of analyses, and guidance to the independent data safety and monitoring committee as to potential course of action if the stopping boundaries are crossed or approached.
(f) Method(s) of randomization (simple, block, minimization, adaptive, etc.) including, if appropriate, strata levels, methods of allocation concealment (central randomization), and outcome adjudication.

These are just a few of the criteria which underpin the design, conduct and interpretation of phase III trials, and the level of detail required in their construction and operation is far more extensive that what is usually required or implemented in the phase II setting.

Many Randomized Phase II or a Randomized Phase III Designs?

The question arises as to whether pooling the information from many randomized phase II designs with a common intervention and similar comparators would provide similar information than a few randomized phase III trials. Table 25.3 highlights some of the differences in the scientific principles between the two types of designs.

From Table 25.3, we see that even though phase II and phase III trials may have common endpoints, the question as to which approach is more desirable is now widely discussed. In Fig. 25.6 the major increase (>4-fold in 2010, 2011), in randomized phase II studies is outstripping the expected conversion of these studies into the phase III setting. There is now a danger that results from randomized phase II trials,

Table 25.3 Explanatory or pragmatic objectives: distinction between randomized phase II and phase II trials

	Randomized design	
	Phase II	Phase III
Aim	Proof of concept/feasibility	Efficacy of therapy
Treatment delivery	Multiple dose titrations (escalations/reductions) permitted	Strict policy on dose delivery
	Focus on tolerability of the intervention. Treatment delivery under optimal conditions	Delivery of intervention in conjunction with routine clinical care
Patient population	Homogeneous population	Wider spectrum of patients with the disease of interest
Sample sizes	Small and based on benefits seen in historical controls	Often large and based on contemporary results (published or pilot phase II/III populations)
Study conduct	Strict protocol adherence, frequent and extensive patient monitoring	Flexibility to interpretation of protocol descriptions often allowed. Pragmatic intent of treatment delivery
Statistical analysis	Exploratory and by treatment exposure. Formal comparisons by randomized groups uncommon (as studies are underpowered). Emphasis on activity of the interventions(s) and their value in subsequent phase III trials	By intention-to-treat with strict rules requiring adjustment for multiple comparisons, interim analyses
	Exploratory results suggesting further investigation of interventions(s) may be warranted	Emphasis on clinical benefit and statistical significance Analyses guided by pre-specified statistical analysis plans Confirmatory results which may change clinical practice
Cost	Steadily escalating as more novel therapies are being investigated, requiring monitoring involving new technologies (MRI, PET) with high frequency. Usually <US $1 M	Can be in the order of tens to hundreds of US $Ms, incorporating clinical, biological, economic, and quality of life analyses
Time frame	Generally completed within 2 years	Rarely completed within 2 years

delivered "fast and furious" to investigators at a containable cost, are regarded as being as robust as their phase III counterparts. A strategy for moving forward is more consideration to phase II/III designs where early signals of activity, potentially based on surrogate outcomes, are embedded in larger phase III trials [48]. These randomized phase III designs have adequate statistical power for traditional clinical outcomes and contain a phase II component in which the strength of surrogates (biomarker levels, tumor shrinkage, delay in disease progression) can be evaluated early and the study continues if thresholds for activity are met. Such designs substantially reduce (1) the time taken to complete studies to evaluate promising therapies and (2) the burden of having to complete and evaluate a phase II trial and then commencing a separate phase III study – the phase II/III design allows for the momentum among investigators and participating sites to be maintained. The phase III trial, OUTBACK [49] of chemoradiation with/without adjuvant chemotherapy for locally advanced cervical carcinoma, has overall survival as its primary outcome with 235 deaths expected. However, a futility analysis is planned after 135 progressions (phase II portion of the design) to decide on whether it is worthwhile for the phase III study to continue.

These designs differ from phase II/III trials focusing on picking the winners (or dropping the losers) from contending investigational therapies in a phase II setting to the phase III setting [50, 51]. The proposed phase II/III design paradigm has many scientific, clinical, and operational advantages. However, more research is required on some of the statistical issues arising when implementing such designs. If, for example, overall survival is the primary outcome and progression-free survival the surrogate, as these outcomes are correlated, exactly what final significance level should be used is unclear. Nevertheless, these hybrid designs show promise in bridging the gap between the phase II and phase III settings to expedite clinical answers more efficiently than current scientific models.

Is There a Role for Randomized Phase III Trials in a World Moving Toward Individualized Medicine?

The completion of the genetic sequencing of the human genome has yielded a rich environment for investigating characteristics of disease over and above traditional prognostic factors coming from patient (such as age, body mass index, race, physiological attributes, etc.) and disease (stage, tumor size, tumor grade, etc.) characteristics. Although the emergence of biomarker characteristics is quite recent in gynecological malignancies (with the exception of CA125 levels which have been of interest over the past 25 years), the prognostic value of estrogen receptor status has been of interest for over the past 50 years. By its nature, individualized medicine suggests that potential treatments are tailored to patients characterized by disease conditions (such as metastases), patient characteristics (such as race, gender), disease aggressiveness and spread (grade, stage), and biological/molecular disposition (biomarker/genetic expression). This last component is currently receiving immense

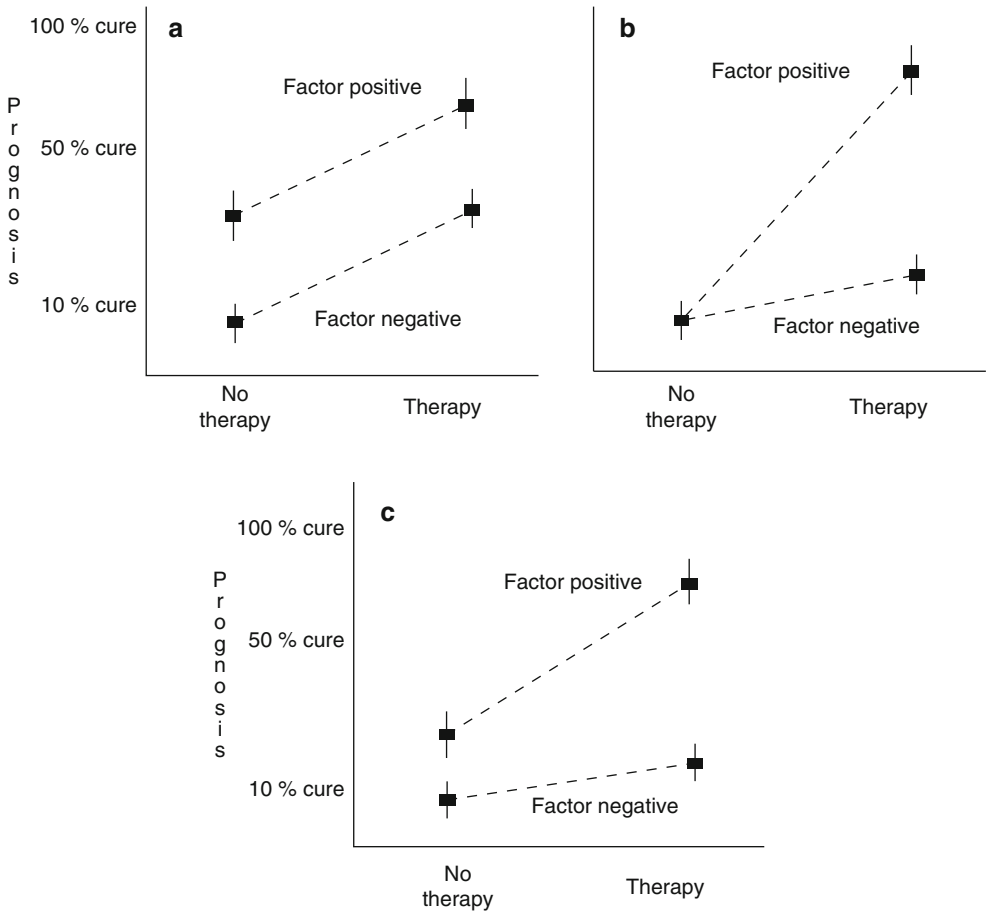

Fig. 25.8 (**a**) Pure prognostic factor – assumes positive factor has favorable prognosis, (**b**) pure predictive factor – assumes positive factor does not have a favorable prognosis but responds to therapy, (**c**) mixed predictive and prognostic factor – assumes positive factor has a more favorable prognosis as well as a differential response to treatment (Adapted from Hayes et al. [55])

interest with the an enormous biological effort to identify and investigate new molecular pathways or to identify genetic mutations especially via genome-wide association studies (GWAS) [52].

As characteristics of many biomarkers can potentially be modified by therapies which in turn alter outcomes, it is instructive at this juncture to distinguish between *prognostic* and *predictive* factors [53, 54]. A prognostic factor is one which is related to outcome regardless of the treatment/interventions. Thus, for example, if for a particular disease, patients of Asian origin have an increased mortality risk compared to Caucasian patients; even though an intervention may reduce the overall mortality, race will still be a prognostic factor. Thus, prognostic factors classify patient's risk of a clinical event based on their baseline risk. Predictive factors on the other hand can be mediated by treatment to reduce the risk of clinical events. For example, in the C017 trial [26], K-ras wild-type patients receiving cetuximab showed a significant survival benefit compared to (1) wild-type patients receiving placebo and (2) to the K-ras mutant group receiving cetuximab. Figure 25.8 shows the difference between prognostic and predictive factors [55]. Personalized medicine aims at identifying predictive factors and tailoring treatment according to the patient's profile of these predictive factors.

Enrichment Designs

Traditionally, the belief has been that patients who are classified as having a positive biomarker (whether a biochemical (over) expression or genetic mutation) will have a better/worse outcomes than those who do not. Women with estrogen receptor-positive breast cancers are generally prescribed a course of endocrine treatment (tamoxifen, aromatase inhibitor), and more recently, those women breast tumors with an overexpression of the HER2 protein from the HER2/neu receptor (a member of the class I RTK (receptor tyrosine kinase) family) would normally be given trastuzumab, a monoclonal antibody that acts on the HER2/neu receptor. The model is that a test for HER2 overexpression is performed and women who test positive to this protein are prescribed trastuzumab. Figure 25.9a shows the study design of the NASBP B31trial, comprising of some 3,351 patients, with the results in Fig. 25.9b [56].

The tissue blocks were re-assayed centrally, and some 17 % of patients were classified as being HER2–. When this group was reanalyzed, the disease-free survival benefit of these patients receiving trastuzumab was similar to the whole cohort [57, 58] (Fig. 25.10).

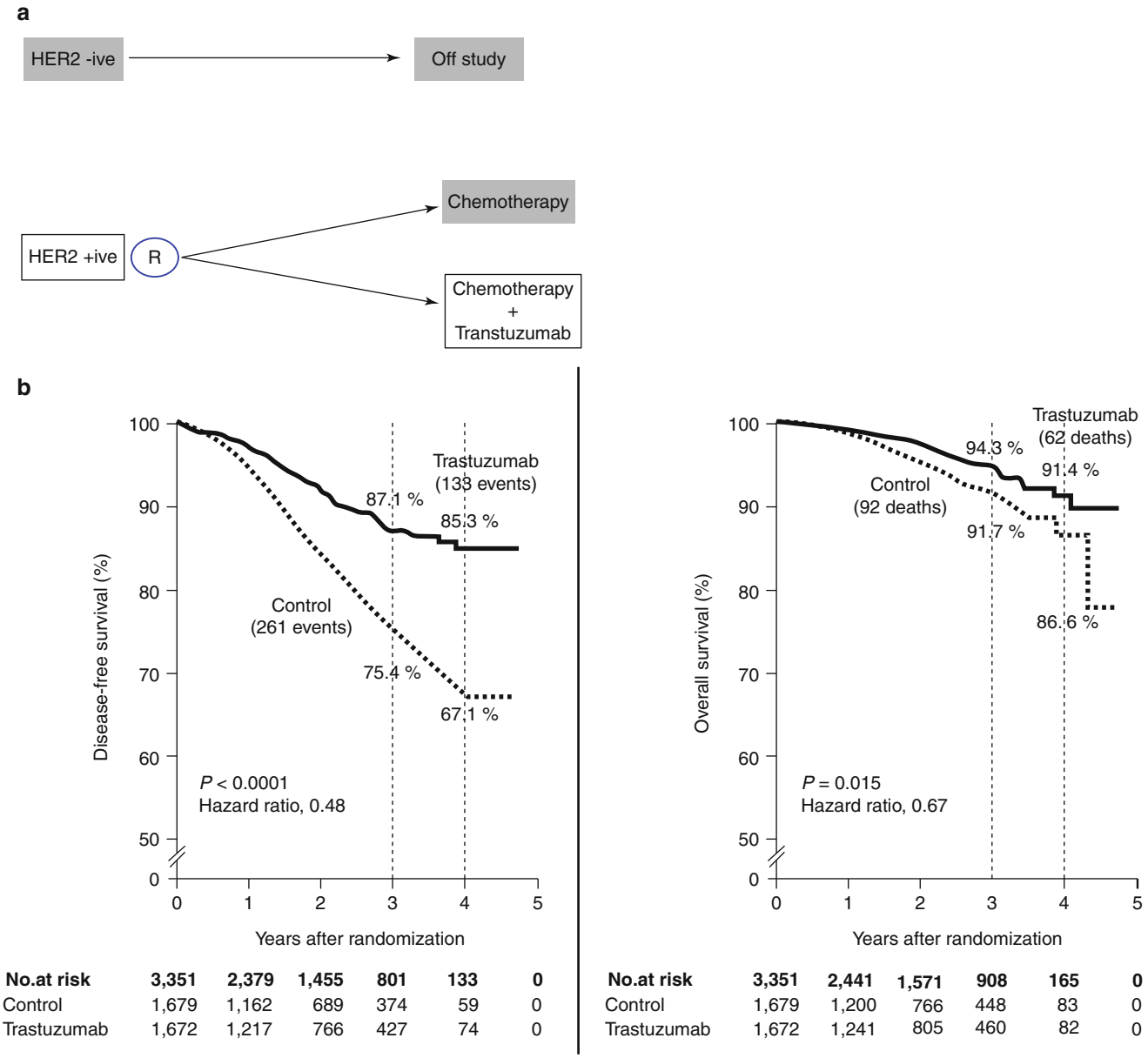

Fig. 25.9 NSABP B-31 trial: (**a**) study design, (**b**) results (From Ref. [56])

This evidence triggered the NSAPB B-47 study where HER2– women are randomized to chemotherapy with trastuzumab compared to chemotherapy alone. These results demonstrate that tailoring treatment solely on the basis that the patient has a druggable target may not always be sufficient. In the HER2 scenario, study designs based on an enriched population (i.e., the HER2+ group) turned out to be suboptimal, and a design enrolling all patients may have been more optimal. Similar patterns are emerging in lung cancer trials looking at tyrosine kinase inhibitors (TKI) in patients with lung cancer. The druggable target in this case is epidermal growth factor receptors (EGFR), and patients with EGFR mutations are predicted to benefit. The SATURN trial [59] showed a significant survival benefit for patients receiving a TKI in the EGFR wild-type subgroup. Trials based on enrichment designs may seriously miss treatment benefits by omitting patients who may have potentially benefited from treatment because of an incomplete understanding of the biology and the mechanism of action of the proposed targeted intervention

Unselected Designs

Unselected designs accept all eligible patients into the study regardless of their biomarker status. If the status can be determined quickly and easily prior to study entry, the biomarker classification should be a stratification factor in the

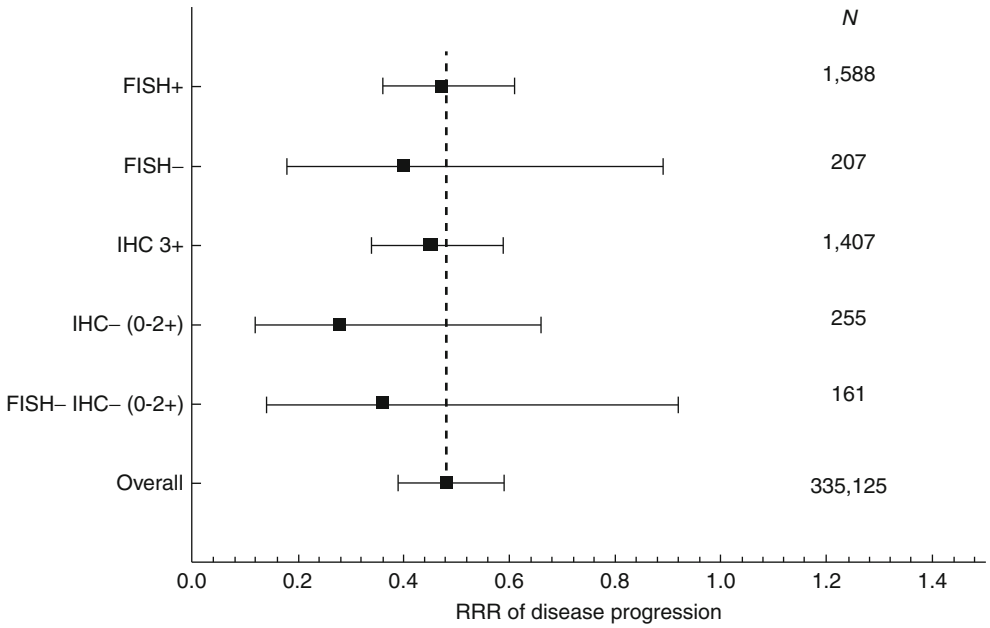

Fig. 25.10 Relative reduction in the risk of disease progression for patient HER2 status in the NSABP B31 trial (Adapted from Paik et al. [57])

trial. More commonly, the biomarker status would be determined post-randomization. Proposed trial designs in this context [60] can be summarized as follows:

(a) *Marker by treatment interaction designs*: In these designs, all patients in the trial will be randomized to the intervention or control therapy. Eligible patients have their biomarker status determined prior to randomization. Marker status is a stratification factor in the randomization, and at the analysis stage, the *treatment by biomarker interaction* will provide evidence of the predictive value of the biomarker. The drawback in such designs is to ensure that the sample sizes are sufficient to have adequate statistical power for the interaction test. This design allows for selective entry into a study – if the prevalence, for example, of the biomarker(-) level is high, then, once this strata level has reached its accrual target, accrual can be curtailed and patients enrolled into the biomarker(+) strata to achieve the required sample size.

(b) *Marker-based strategy designs*: The biomarker status for eligible patients is determined prior to study enrollment. Two options present themselves: (1) randomization will be only for patients with the desired biomarker levels and others will not be enrolled into the study as was the case with the NSABP B-31 trial and (2) patients are randomized into one of two treatment strategies. The first strategy is to treat patients with the targeted therapy or standard care depending on their biomarker status. The second strategy is a second randomization for patients to receive targeted therapy or standard treatment irrespective of their biomarker status. This design can be useful if the evidence to limit treatment to just the biomarker + (or −) patients is unclear.

Hybrid Designs

Studies aimed to incorporate patients' risk profiles into treatment strategies fall into this category. Genetic signatures and/or risk score models (prognostic nomograms) [61] generally risk stratify patients into two or three groups high/low or high/intermediate/low. With three groups, to evaluate the benefit of risk scores or gene signatures, a number of possibilities present themselves [62], viz.,

(a) A six-arm trial evaluating the benefit of (targeted) interventions separately in each of the groups. While such an evaluation would be a major undertaking with substantial financial overheads, the scientific information provided from such studies could potentially be practice changing and allow for more efficient targeting of therapies for improved clinical benefit.

(b) A selective design where patients classified at high risk or low risk will receive the corresponding standard therapy, while those in the intermediate group are randomized to receive either therapy recommended for low-risk patients or that for high-risk patients. As well as comparing the randomized groups, selective comparisons can also be made between the various therapies in all of the three risk groups. This design can help identify optimal treatment in the intermediate group but assumes that optimal treatment in the high- and low-risk groups has already been determined.

Variations of these designs can occur when patients' risk is classified both by genetic signatures and prognostic nomograms (usually containing clinical characteristics). The MINDACT trial in breast cancer [63] seeks to evaluate a 70-gene signature classifier with clinical prognosis with the

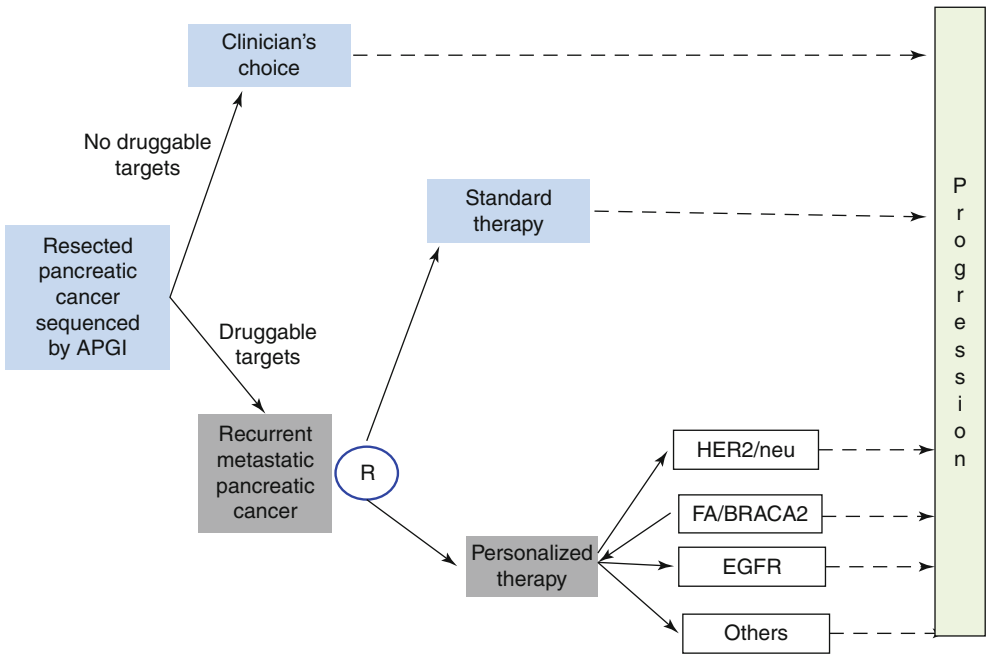

Fig. 25.11 The IMPACT trial design to evaluate the benefit of a strategy to incorporate personalized therapy

aim of evaluating treatment benefit based on a genetic-guided profile.

Trials need not necessarily be one related to molecular/genetic overexpressions. In a study design for operable esophageal carcinoma, patients receive standard neoadjuvant chemotherapy followed by a PET scan after 14 days. For those responding according to PET, the chemotherapy is continued for a second cycle prior to surgery, while for those not responding, there is a randomization to two cycles of either induction chemotherapy or chemoradiation prior to surgery. In this design, the PET scan is the diagnostic tool to identify early nonresponders in the treatment course with an objective to evaluate the benefit of switching treatment modality (chemoradiation) on pathological response.

Multiple Targets

While single biomarkers are still currently favored by investigators, designs focusing on single but potentially different biomarkers have been suggested to gain maximum benefit from patient populations having different molecular targets for the same disease. The BATTLE trial design [64–66] aims to evaluate multiple molecular targets in advanced lung cancer by developing a hierarchy of biomarkers. In this design, four biomarker classes are ordered: EGFR mutation/amplification, K-ras and/or B-raf mutation, VEGF and/or VEGFR expression, and RXR and/or cyclin D1 expression. Patients with multiple biomarker expressions will receive treatment based on the above hierarchy, so, for example, if a patient has a K-ras mutation and VEGFR expression, treatment will be tailored to the K-ras mutation. The design seeks to minimize patient accrual into those treatments which do not appear promising using an adaptive (outcome-based) algorithm.

A second design that enrolls patients with various molecular profiles is the Individualized Molecular Pancreatic Cancer Therapy (IMPACT) trial being developed by the Australian Pancreatic Cancer Genome Initiative (APGI) together with the Australasian Gastro-Intestinal Trials Group (AGITG). In this design, patients with operable pancreatic cancer agree to have their tumors sequenced and tested. This identifies a subset of patients which have biomarker expressions that allow them to be targeted in the event of disease progression or recurrence. On recurrence patients with druggable targets are randomized to receive either standard treatment (gemcitabine) or combination therapy including the appropriate targeted therapy. The design is illustrated in Fig. 25.11.

This design will allow for an evaluation of both the value of a personalized approach and identify in which biomarker targets such an approach would be of benefit. A similar design has been proposed in the I-SPY2 study [67] examining multiple biomarker signatures in breast cancer. Combinations of HER2, hormone receptor status, and MammaPrint signature are investigated through an adaptive randomized design [51].

Same Targets Different Disease Sites

When designing biomarker studies, one reasonable question is whether studies should be disease or molecular target specific. After all, why should patients with EGFR+ ovarian

cancers not benefit from a TKI which has been shown to be efficacious in non-small cell lung cancer? Should trials be designed investigating the benefit of targeted treatment in patients whose tumors overexpress the targets of interest? This would certainly allow more patients to be accrued faster, and if the biologic hypothesis is correct, results on treatment benefit would flow more rapidly into clinical practice. This design would be the complement of the IMPACT study (Fig. 25.11). Instead of a disease site (pancreatic), we have a single target (BRACA1, EGFR+, hENT1+, etc.) and stratify by disease site (ovary, lung, pancreas). This biomarker-driven design has the potential for investigating benefit over a wide range of disease conditions and reducing the pressure to study small numbers of patients with so-called rare tumors. Unfortunately the evidence to embark on such designs has not been entirely promising so far. Figure 25.12 shows the waterfall plots for the response to PLX4032, an oral BRAF kinase inhibitor in patients with melanoma [68] and colorectal cancer [69].

Among those patients diagnosed with melanoma 81 % (26/32) patients responded (partial or complete) to the BRAF inhibitor. While those patients who were diagnosed with colorectal cancer with the same target and treated with the same compound only demonstrated a 5 % response (1/19). Current molecularly targeted interventions as yet have not demonstrated consistent benefit over multiple disease sites. The value of conducting trials involving multiple disease sites with the same target remains to be proven.

Surrogate Endpoints

With the emergence of new targeted therapies, changes in biomarker levels are usually thought to be strong signals of treatment benefit. Thus, in the treatment of ovarian cancer, a normalization of CA125 levels is commonly regarded as tumor control resulting in prolonged progression-free and overall survival. While CA125 has not yet been validated as a surrogate marker, it is possibly a surrogate marker for tumor progression and overall survival. While there is a wealth of literature on the desirable properties of surrogate outcomes, it is instructive to highlight some of the properties for biomarkers to satisfy in order to be useful surrogates [70]. Surrogate outcomes are intermediate events/measurements observed prior to clinical outcomes which can replace clinical outcomes as measures of the effectiveness of intervention(s) and are strongly related to the clinical outcome(s) of interest. Thus, if the outcome of interest is overall survival (OS), progression-free survival could be thought of as a surrogate which is an intermediate event and strongly (although not perfectly) correlated to OS as illustrated in Fig. 25.13. For surrogates to be useful, the following properties need to be satisfied:

(a) The intervention must have a systematic effect on both the surrogate and clinical outcomes.

(b) The effect that the intervention has on the clinical outcome can be entirely and demonstrably attributed to effect of the intervention has on the surrogate outcome.

Serum or other biomarkers which are good surrogates for clinical outcomes may be both predictive and prognostic. These principles have been recently illustrated in a randomized trial examining the value of the mTOR inhibitor temsirolimus in the treatment of renal carcinoma where cholesterol levels are predictive markers of PFS and OS [71]:

1. Temsirolimus was associated with significant survival and progression-free survival benefit in an unadjusted analysis.
2. When adjusted for changes in cholesterol, the treatment effect disappears for both PFS and OS.
3. Baseline cholesterol levels were significantly related to PFS and OS in univariate and multivariate analyses.
4. The treatment effect for OS and PFS was not significant when changes in cholesterol levels were included as time-dependent variables.

These steps are key in demonstrating that a biomarker may be a potential surrogate for outcome. Once biomarker(s) which can serve as surrogate outcome measures has been identified, there is often pressure to implement these findings without thorough evaluation. Potential surrogates would be levels of circulating tumor cells through known biomarkers CA125, PSA levels, Ki67 proliferation, tumor regression, or disease progression.

Should Large-Scale Phase III Studies Continue to Be Designed and Conducted?

One of the limitations in the development of efficient trial designs for evaluating individualized treatment approaches is the limited experience with appropriate evidence-based designs. A number of design issues still need to be addressed:

1. Is the evidence of treatment of molecular targets strong enough to personalize medicine and abandon phase III trials – not at this time. New study designs such as the IMPACT, I-SPY2, and BATTLE will likely provide some new insights into innovative methodological approaches for evaluating targeted therapies.
2. Some of the early adaptive designs have exhibited a greater than anticipated potential for abandoning therapies which may in fact be efficacious, due to small sample sizes, variability (assays, patients), and patient selection (multiple versus single targets).
3. Whether the multitude of biomarker designs will ever have sufficient statistical power to detect small but clinically relevant treatment-biomarker interaction effects remains to be seen. There is a danger that large signals in small trials will dominate research interests with a diminishing interest in conducting the adequately powered phase III trial. This may inevitably lead to disappointment when the results in clinical practice do not measure up to those seen in the preliminary studies.

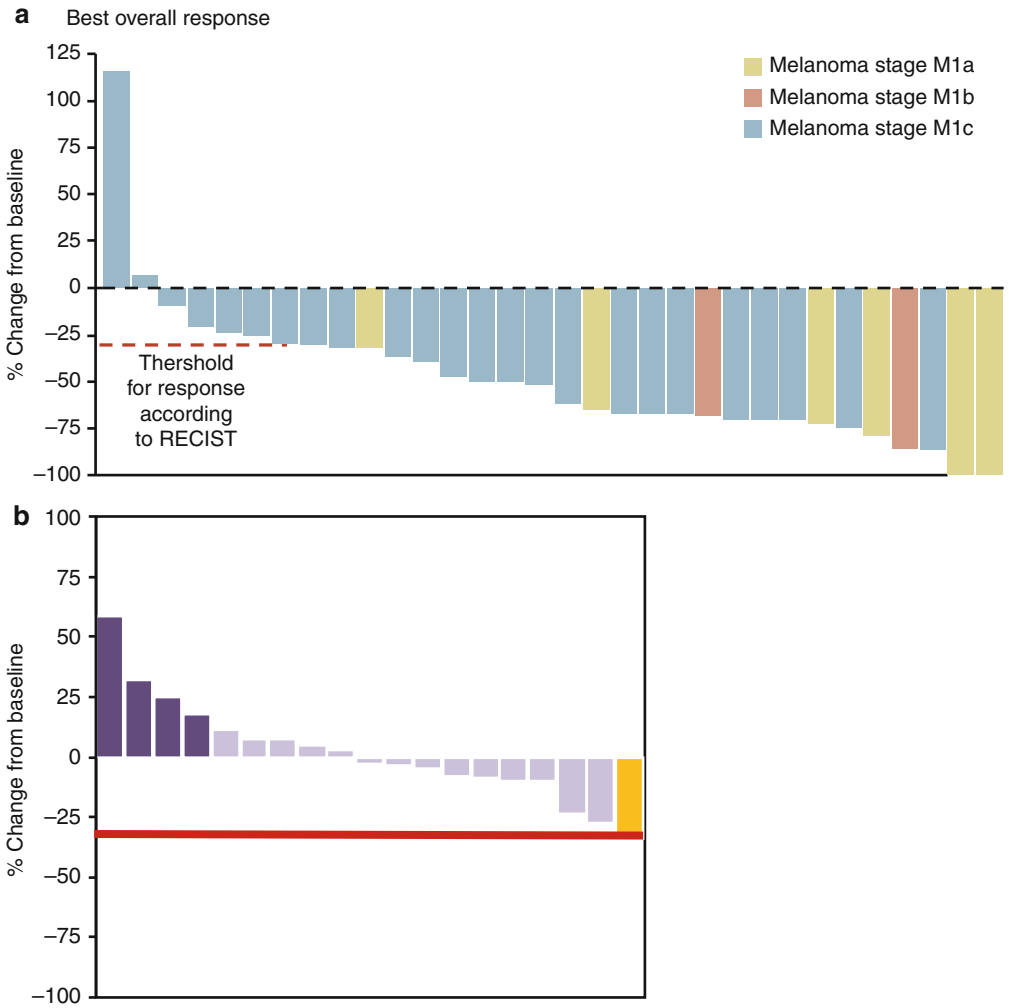

Fig. 25.12 Waterfall plots of response according to RECIST for patients with BRAF mutations: melanoma and colorectal cancer (From (**a**) Ref. [68] and (**b**) Ref. [69])

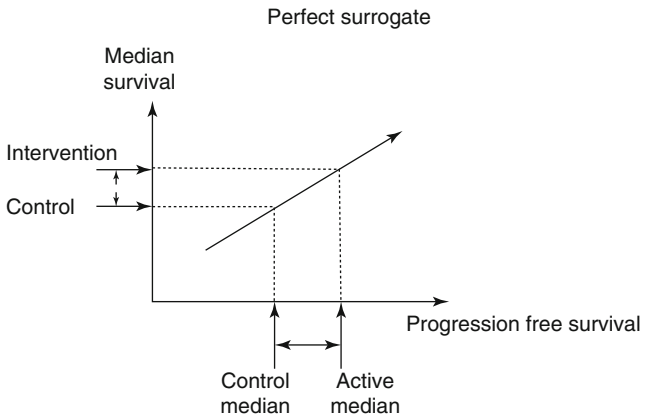

Fig. 25.13 Relationship between outcomes (PFS and OS) for a perfect surrogate

4. How much should trials of personalized therapies medicine be required to impact on overall survival rather than just delay disease progression? Benefits from targeted agents in metastatic colorectal and lung cancer have had little impact on survival improvement. There is a danger that the new molecular therapies will end up being a costly strategy to prolong PFS will little gain in the patient's ultimate survival outcome.
5. There is a need for a concerted effort to investigate the benefit of targeted therapies in the neoadjuvant setting (in disease lending themselves to surgical or radiation therapy modalities). This could involve tumor assays/sequencing during the neoadjuvant course and from the tumor at surgery. Changes in the biological profile would help with patient selection (a) postsurgery, (b) at relapse, and (c) for post-second-line treatment.
6. There is a need to develop methodology for discerning clinically relevant treatment benefits within groups of patients who are identified by their biomarker levels that relax the requirement of large sample sizes.

Currently, there is overwhelming evidence for biomarker-driven therapies to be evaluated with a phase III framework. The overwhelming approach in trials in gynecological oncology is still disease focused with tissue collection and the molecular profiling being secondary. There is a need to shift this focus to include in the next generation of trials biomarker profiling as an integral part of the scientific question. Additionally, patient

selection based on risk profiles needs to be considered. In the past 2 years, there were over 60 publications developing risk profiles/nomograms in oncology, yet only a handful of protocols employ these to select patients into studies. Risk profiles together with biomarker levels may help identify a larger population of patients who may benefit from targeted therapies.

Concluding Comments

- Biomarker-driven therapy in gynecological malignancies is rapidly increasing, and the appropriate study designs will be required to evaluate the potential effectiveness of new discoveries.
- The development and refinement of such designs will however require a much closer interaction with molecular biologists, clinical scientists, clinical practitioners, bioinformaticians, and biostatisticians. Biostatisticians in particular will need to become intimately involved with designs of the genome-wide association studies (GWAS) being performed in this disease to ensure robustness of the associated findings.
- New designs being proposed (especially adaptive) need to be adopted with caution – many proposed approaches rely heavily on untested assumptions (e.g., beta priors, unrealistic effect sizes) with rationale being driven by extensive simulation rather than clinical experience.
- Overoptimistic interpretation of early results, especially when applied to surrogate outcomes, can potentially result in disappointment later on in the research cycle. This has been evident in the advances improving progression-free survival but no subsequent overall survival benefit being demonstrated.
- The challenge is now to incorporate individualized therapies into large-scale clinical studies. Such trials have been championed in cardiovascular disease [72] and hypertension, enabling major advances to be made by providing sufficient statistical power to identify modest but important differences in the treatment regimens. Such trials in gynecological malignancies would provide insight into mechanisms of action at both clinical and biological levels, including identification of potential biomarker/treatment interactions, subgroups of patients who benefit most, and biomarker combinations which may be most effective.

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How Should Early Gestational Trophoblastic Disease Be Managed?

26

Linda G.W. Kerkmeijer and Julian C. Schink

Summary Points

- Can HCG follow-up be discontinued after normalization of HCG levels following molar evacuation in patients with low risk of persistent trophoblastic disease?
- Should the management of trophoblastic disease be conducted at specialized centers?
- What type of imaging is optimal for evaluation of patients with postmolar trophoblastic neoplasia?
- Should low-risk persistent trophoblastic disease be treated with single-agent methotrexate?
- Can we predict resistance to single-agent chemotherapy in patients with low-risk persistent trophoblastic disease?
- Is a second curettage useful in low-risk persistent trophoblastic disease?

Introduction

Gestational trophoblastic disease (GTD) describes a heterogeneous group of disorders characterized by abnormal proliferation of the placental trophoblast (Table 26.1) [1]. Complete and partial hydatidiform moles result from abnormal fertilization and are benign, but may progress to malignant gestational trophoblastic neoplasms (GTN), including invasive mole, choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [2]. Hydatidiform mole has an incidence of approximately 1 in 1,000 pregnancies, with some geographical variation [3]. Although GTN most commonly develops after molar pregnancy, it may also arise from normal gestation. CCA occurs in approximately 1 in 40,000 pregnancies and 1 in 40 hydatidiform moles, though these rates are much higher in Asia [4]. GTN is one of the most curable malignancies in women, even when metastatic disease is present, due to its sensitivity to chemotherapy.

Earlier diagnosis of GTD has been made possible by accurate and sensitive tests for human chorionic gonadotropin (HCG), which is produced primarily by the syncytiotrophoblast cells. Except for PSTT, all subtypes of GTD produce high levels of HCG [5]. Persistent GTD is diagnosed based on a rise in blood HCG levels after molar evacuation. HCG levels have been incorporated into the International Federation of Gynecology and Obstetrics (FIGO) prognostic scoring system for persistent GTD, with the lowest risk associated with HCG <1,000 IU/L (Table 26.2) [6]. The HCG present in GTD is a heterogeneous mix of complete HCG, nicked HCG, and free α- and β-subunits; thus, HCG assays must detect all forms of HCG and its subunits in order to accurately diagnose active GTD [7]. The variation among commercially available HCG assays makes it difficult to compare HCG measurements between assays. False-positive HCG measurements can also occur due to the presence of heterophilic antibodies in the blood: human anti-mouse antibody (HAMA) reacts with the mouse immunoglobulins that are used in HCG assays. Because HAMA is not excreted in the urine, a simultaneous urine HCG measurement should be performed to determine whether the blood HCG value is a false-positive and to prevent unnecessary treatment for presumed GTD.

In this chapter, we will discuss controversial areas in the management of low-risk GTD (specifically hydatidiform mole, low-risk persistent GTD, and nonmetastatic PSTT).

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Table 26.1 Clinical and pathologic features of GTD

GTD	Pathology	Clinical presentation
CHM	46,XX; 46,XY	15–20 % trophoblastic sequelae
	No fetus/embryo	HCG usually >100,000 IU/L
	Diffuse swelling of villi	Theca-lutein ovarian cysts on ultrasound
	Diffuse trophoblastic hyperplasia	Vaginal bleeding
		Excessive uterine size
		Hyperemesis gravidarum
		Preeclampsia
		Hyperthyroidism
		Respiratory insufficiency
PHM	Triploid	<5 % trophoblastic sequelae
	Abnormal fetus/embryo	HCG often <100,000 IU/L
	Focal swelling of villi	Symptoms of missed or incomplete abortion
	Focal trophoblastic hyperplasia	
Invasive mole	Myometrial invasion	Elevated HCG
	Swollen villi	Intraperitoneal bleeding
	Hyperplastic trophoblast	Vaginal hemorrhage
		15 % metastatic (lung/vagina)
CCA	Abnormal trophoblastic hyperplasia and anaplasia	Elevated HCG
	No villi	Vascular spread to lung/brain/liver
	Hemorrhage	Malignant disease
	Necrosis	Bleeding from metastases
PSTT	Tumor cells infiltrating myometrium	Rare
	Vascular/lymphatic invasion	Nonmetastatic
	Intermediate cells	Resistant to chemotherapy
	No villi	
	Some hemorrhage and necrosis	
	Tumor cells hPL-positive	

Table adapted from Lurain [1]
GTD gestational trophoblastic disease, *CHM* complete hydatidiform mole, *PHM* partial hydatidiform mole, *CCA* choriocarcinoma, *PSTT* placenta site trophoblastic tumor, *HCG* human chorionic gonadotropin

Table 26.2 FIGO 2000 prognostic scoring system for GTN

FIGO score	0	1	2	4
Age	≤40	>40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4–<7	7–<13	≥13
Pretreatment HCG IU/L	$<10^3$	10^3–$<10^4$	10^4–$<10^5$	$\geq 10^5$
Largest tumor size including uterus	–	3–<5 cm	≥5 cm	–
Site of metastases	Lung	Spleen	Gastro	Brain
		Kidney	Intestinal	Liver
Number of metastases identified	0	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single-agent	>1

Reprinted from FIGO staging for gestational trophoblastic neoplasia 2000 [6] with permission from Elsevier

Hydatidiform Mole

Complete Hydatidiform Mole (CHM)

Today, most complete molar pregnancies are diagnosed early, in the first trimester of pregnancy, based on symptoms of vaginal bleeding, elevated HCG, or by ultrasound examination. With earlier diagnosis, the characteristic clinical features of CHM are less often present [8, 9]. Complete HM is generally diagnosed by a characteristic vesicular pattern on ultrasound, which may be less marked in early CHM. Macroscopically, CHM presents as enlargement of villi with widespread trophoblastic hyperplasia in the absence of embryonic or fetal tissues. It consists of syncytio- and cytotrophoblast cells, and

fetal blood vessels are usually absent, except in cases of very early CHM [10]. CHM have an androgenetic diploid karyotype (46,XX; 46,XY) due to either reduplication of the sperm haploid genome (23,X) in a fertilized, enucleated oocyte or the fertilization of an enucleated oocyte with two sperm. Flow cytometry can be useful to differentiate between diploid CHM and triploid partial hydatidiform mole (PHM) [11]. Immunohistochemical analysis for expression of a maternally imprinted gene, p57kip, can reliably differentiate complete moles from hydropic abortion.

Partial Hydatidiform Mole (PHM)

The clinical presentation of PHM is less marked than CHM; in general, patients with PHM present late in the first or early in the second trimester with signs and symptoms of a missed or incomplete abortion [10]. Pre-evacuation HCG levels are usually lower than those in complete HM. The ultrasound pattern in PHM is also less consistent and depends on careful measurement of the gestational sac and detection of cystic changes in the placenta. Macroscopically, PHM shows hydatidiform villi with mild trophoblastic hyperplasia and normal chorionic villi. Fetal blood vessels are often present and embryonic structures may be found. In the first trimester, these features may be more subtle. PHM are commonly triploid and biparental (69,XXX or 69,XXY), originating either from fertilization of a normal ovum by a single sperm followed by reduplication of the haploid paternal genome or from dispermic fertilization.

Management of Hydatidiform Mole

Earlier diagnosis of molar pregnancy, when there is lower risk of progression to malignancy, increases the likelihood of cure. The preferred treatment method is evacuation of the uterine cavity by suction curettage with ultrasound guidance. Sharp curettage alone may perforate the uterus in case of invasion of the myometrium and is therefore discouraged. Medical induction by prostaglandin or oxytocin is avoided, as it has been associated with an increased risk of the need for adjuvant chemotherapy due to a higher risk of dissemination of trophoblastic cells and of pulmonary trophoblastic emboli to the lungs [12]. In case of severe bleeding following suction curettage, a single dose of ergotamine may be effective to stop the bleeding by causing uterine contraction; this approach has not been associated with a higher risk for requiring chemotherapy when used after molar evacuation. After molar evacuation, a baseline chest x-ray should be performed and patients should be monitored with serial serum HCG levels in order to detect persistent GTD and the development of GTN. Patients with a history of molar pregnancies are at increased risk (approximately 1 %) of another molar pregnancy; therefore, close follow-up with serial HCG measurements and ultrasound is recommended for all future pregnancies [13].

Although the diagnosis and management of molar pregnancy are fairly standard, there are some outstanding controversies, which are discussed here.

What Is the Optimal Contraceptive Regimen for Women After Molar Evacuation?

After CHM or PHM, patients are counseled to use contraception during the follow-up period. Use of intrauterine devices should be delayed until after HCG levels have returned to normal in order to reduce the risk of uterine perforation, bleeding, and infection. There is some controversy regarding the use of oral contraceptives after molar evacuation, as one study reported an increased risk of postmolar GTD [14]. Subsequently, two large studies found that postmolar GTD is not associated with oral contraceptive use [15, 16]; specifically, that oral contraceptives containing less than 50 mg estrogen are not associated with an increased risk [17]. These findings suggested that the risk of postmolar GTD is related to the dose of estrogen in oral contraceptives, which should be taken into account when counseling patients regarding their contraceptive choices after a molar pregnancy.

Should a Hysterectomy Be Performed in Patients with Persistent Low-Level HCG but Without Clinical Evidence of Trophoblastic Tumor?

Most cases of persistent GTD and postmolar GTN are detected during incidental pregnancy testing or during HCG follow-up monitoring. In a small proportion of the population, however, persistent low HCG levels are present that are not caused by heterophilic antibodies or cross-reactivity with TSH or LH in pituitary disease, and there is no clinical evidence for pregnancy or uterine or metastatic GTD [18, 19]. This phenomenon of a "true" low-level HCG is called quiescent GTD. There is no standard procedure used to differentiate between quiescent and active GTD in patients with persistent low-level HCG. Nevertheless, GTN may develop in some patients, even several years after molar evacuation, and continued follow-up is essential in order to detect and treat these tumors early. Because women with quiescent GTD do not respond to single-agent chemotherapy, and multi-agent chemotherapy is not justified in the absence of identifiable GTN [19–21], is it then reasonable to perform hysterectomy to reduce the risk of persistent GTD and GTN?

Table 26.3 FIGO 2000 criteria for diagnosis of persistent GTD

1. HCG plateau lasting for four measurements over a period of at least 3 weeks (days 1, 7, 14, and 21)
2. Rise in HCG of 10 % or more for three measurements over at least 2 weeks (days 1, 7, and 14)
3. Persistence of elevated HCG 6 months after mole evacuation
4. Presence of a histological diagnosis of CCA

Reprinted from FIGO staging for gestational trophoblastic neoplasia 2000 [6] with permission from Elsevier

PSTT is not associated with elevated HCG and may be missed during normal postmolar follow-up, especially in women with slowly rising HCG levels. Hysterectomy might therefore be justified to remove the risk of PSTT in patients who do not wish to preserve fertility. This approach is supported by a case report from the Charing Cross Hospital, London, UK, in which a patient with slowly rising HCG levels but no clinical signs or symptoms and no disease found with imaging or histological evaluation of curettage specimens underwent hysterectomy and was found to have PSTT [22].

Conversely, a major surgical intervention may not be justified in the absence of evidence of localized or metastatic GTN. The majority of patients with quiescent GTD will likely undergo an unnecessary treatment, as only a small proportion of patients will go on to develop GTN [18, 21, 23, 24]. Treatment should therefore be withheld until the diagnosis of persistent GTD is made according to the FIGO 2000 criteria in patients following molar pregnancy (Table 26.3) or until clinically detectable disease is present. Nevertheless, long-term follow-up should be performed since some patients will develop GTN.

Ultimately, there is no generally accepted gold standard for differentiating between quiescent and active GTD in patients with persistent low-level HCG. Such a marker would be useful in determining whether treatment of these patients is justified. Elevated levels of hyperglycosylated β-HCG, which is produced by the cytotrophoblast and promotes invasion in malignancy and normal pregnancy, has been suggested by one group as a marker for active disease [20, 25], but its potential utility needs to be tested in larger clinical trials.

Can HCG Follow-Up Be Discontinued After Normalization of HCG Levels Following Molar Evacuation in Patients with Low Risk of Persistent GTD?

Discussion regarding the extent of follow-up once postmolar HCG levels have normalized is ongoing. In general, it is recommended that after molar evacuation, HCG levels should be monitored weekly until normal levels have been obtained. In some countries, this is followed by monthly monitoring for 6 months [26, 27]. In other countries, HCG follow-up has been shortened, with monitoring ending when two normal monthly measurements are made [28–30]. Certainly, HCG follow-up increases patient anxiety and stress, delays childbearing in patients who wish to conceive, has a poor compliance rate, and is associated with increased workload and costs [31–33].

Several studies support abbreviated follow-up, as there is a very low risk of recurrent GTD after spontaneous normalization of HCG levels. The majority of studies show no relapsed GTD after HCG normalization [28, 29, 33–38], and some large studies have reported a low incidence of recurrent GTD [27, 30, 39, 40]. In a more recent study of 6,279 patients seen between 1993 and 2003 at the Trophoblastic Disease Centre at the Charing Cross Hospital, only three patients (0.05 %) whose HCG concentrations spontaneously returned to normal levels subsequently developed persistent GTD (after 67, 402, and 1,267 days, respectively) [27]. Similarly, a Dutch study revealed that only 1 of 265 patients relapsed following spontaneous normalization of HCG levels [28]. It is also important to note that the incidence of recurrence after initial HCG normalization depends on the criteria used to define normalization and on the sensitivity of the HCG assays used. Most cases of recurrent GTD (29 out of 33) occurred more than 15 years ago, when HCG assays had a higher detection limit than the assays used today. With the currently available very sensitive HCG assays, it is possible that the incidence of recurrent GTD after normalization of postmolar HCG might be much lower.

Yet even though recurrent GTD is extremely rare, it can be fatal without treatment and has high cure rates with chemotherapy. It can be argued that it is crucial that we detect all relapses of GTD as early as possible. Furthermore, sensitive HCG assays that measure all forms of HCG are not available in all countries, and the use of a less sensitive HCG assay increases the risk of false-negative HCG results. If HCG follow-up is stopped based on false-negative HCG results, there is a risk of missing recurrent GTD that could have been successfully treated at earlier stages. For these reasons, shortening the recommended HCG follow-up period may be safe except in cases in which a less sensitive assay or an assay that does not measure all forms of HCG is used.

Should Prophylactic Chemotherapy Be Given at the Time of Molar Evacuation?

The use of prophylactic chemotherapy to prevent the development of persistent GTD after molar evacuation has been subject of two randomized studies. In the first, a single course of MTX reduced the incidence of persistent GTD in high-risk patients (HCG levels >100,000 IU/L, large-for-date uterine size, and ovarian size >6 cm) from 47.4 % (9/19)

to 14.3 % (3/21) patients ($p < 0.05$) [41]. However, in the persistent GTD patients who received prophylactic chemotherapy and developed persistent GTD afterwards, more courses of chemotherapy were required to achieve disease remission than in patients who had not been exposed to prophylactic chemotherapy [42]. In another randomized trial of 60 high-risk molar pregnancy patients, one course of actinomycin D reduced the risk of persistent GTD from 50 to 14 % ($p = 0.005$) [43]. In both studies, no deaths occurred in the treatment or control groups due to GTD or toxicity [41, 43]. Since not all patients remain free from malignant sequelae, prophylactic chemotherapy does not eliminate the need for HCG follow-up after molar evacuation. Two larger nonrandomized trials confirm these findings [44, 45].

More widespread use of prophylactic chemotherapy remains controversial; the main limitation is that a large proportion of molar pregnancy patients would receive needless chemotherapy and experience the associated toxicity, whereas with adequate HCG follow-up, almost all patients diagnosed with persistent GTD can be cured by chemotherapy. Prophylactic chemotherapy may be justifiable for high-risk molar pregnancy patients in whom HCG follow-up may be difficult (e.g., low expected compliance) [1, 43, 46].

Should the Management of GTD Be Conducted at Specialized Centers?

Centralization of GTD management has become an important issue, particularly because the low incidence of the disease limits the experience of most hospitals. Moreover, GTN is potentially deadly, but has high cure rates in patients who are diagnosed early and treated appropriately. At the very least, all patients with GTD should be registered with a specialist center for HCG surveillance. In 1971, Brewer et al. reported that treatment for GTD at the Trophoblastic Disease Center Chicago was associated with nine times lower morbidity and mortality than treatment in nonspecialized institutions [47]. Patients who were referred to the Brewer Trophoblastic Disease Center with initial treatment failure most commonly had received an inappropriate drug regimen [38, 48]. Data from a worldwide survey showed considerably lower survival rates in countries that do not have centralized management of GTD [49]. The mortality in the United Kingdom, France, and the Netherlands, all of which have centralized GTD management, was significantly less than in the United States. In the Netherlands, there is a central advisory board and centralized follow-up, but treatment takes place at different referral hospitals. Centralization of GTD management also makes it possible to review the histologic diagnosis by specialized pathologists; this is clinically valuable, as it can be difficult to differentiate the subtypes of GTD and interobserver variability is high [50, 51].

Persistent GTD and Low-Risk GTN

Approximately 15 % of CHM and 0.5 % of PHM patients develop postmolar persistent GTD [37, 52]. The most common clinical symptom is vaginal bleeding. Diagnosis of persistent GTD is generally based on consistently elevated or rising HCG levels, per the FIGO 2000 criteria shown in Table 26.3 [6], and abnormal ultrasound following molar evacuation. Histological confirmation of persistent GTD after a molar pregnancy is generally not performed, due to the risk of hemorrhage with uterine evacuation. In patients with persistent GTD, malignant postmolar neoplasias (GTN) are categorized based on histology as invasive mole, CCA, or PSTT. Histopathologically, invasive mole has chorionic villi, CCA is non-villous, and PSTT consists of intermediate trophoblast that infiltrates myometrial tissue. A minority of persistent GTD patients may develop metastatic disease (highly metastatic CCA or less metastatic invasive mole) with abdominal pain or swelling due to intra-abdominal metastatic disease or local progression. While it is important to adhere to the FIGO criteria to diagnose persistent GTD, these criteria do not apply to metastatic GTN. Diagnosis of metastatic GTN is made during postmolar follow-up, with the appearance of brain, liver, or gastrointestinal metastases or radiologic opacities >2 cm on chest x-ray.

Staging, Prognostic Scoring, and Treatment of Persistent GTD

Treatment of persistent GTD is based on anatomic stage and a risk scoring system (Tables 26.2 and 26.4). At present, single-agent chemotherapy, most commonly with methotrexate (MTX) or actinomycin D, is the treatment of choice for patients in the low-risk category (stage I and stage II–III, score <7). In patients initially treated for low-risk GTN, recurrence rates of trophoblastic disease are approximately 3 % [53]. For patients with high-risk disease (stage II–III, score 7 or greater and stage IV), multi-agent chemotherapy is recommended. Hysterectomy may be used in patients with metastatic GTN, and selective use of radiation and surgery is warranted for patients with stage IV disease. Several aspects

Table 26.4 FIGO 2000 anatomical staging of GTN

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

Reprinted from FIGO staging for gestational trophoblastic neoplasia 2000 [6] with permission from Elsevier

of the management of persistent GTD and low-risk GTN remain controversial and are being discussed and rigorously tested in clinical trials. A few of these topics are discussed here.

What Type of Imaging Is Optimal for Evaluation of Patients with Postmolar GTN?

All patients with suspected or established postmolar GTN should undergo a metastatic workup in order to assess prognosis with the FIGO staging system shown in Table 26.2 [6, 54] and select the most effective treatment. The recommended imaging studies for postmolar GTN include a chest x-ray (and if negative, a CT of the chest) as well as CT scans of the abdomen and pelvis, and either CT or MRI of the brain. The vast majority (94 %) of patients with brain metastasis have associated lung metastases; conversely, 20 % of patients with lung metastasis have central nervous system metastasis. Some practitioners chose not to perform a brain scan if the chest is clear, while this strategy is financially prudent it does risk missing 6 % of extremely high-risk patients. The practice at the Brewer Center at Northwestern University is to perform an MRI of the brain during the staging evaluation of all patients with post-molar GTN or choriocarcinoma. Ultrasound of the pelvis or MRI may also help identify patients who would benefit from hysterectomy (Fig. 26.1).

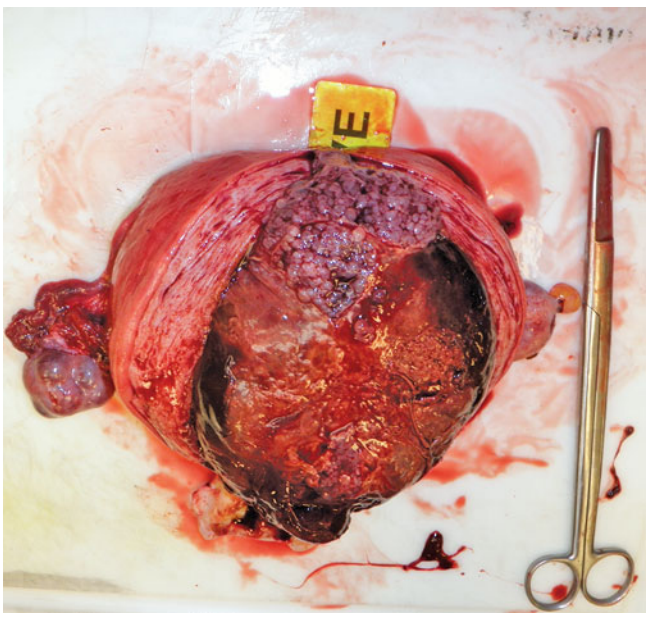

Fig. 26.1 Hysterectomy may prevent the development of post-molar gestational trophoblastic neoplasia in women with significant risk factors such as uterus >16-week size, HCG > 100,000, and theca-lutein cysts as was noted in this case

Should Low-Risk Persistent GTD Be Treated with Single-Agent Methotrexate?

There is no consensus regarding the single-agent chemotherapeutic agent of choice for low-risk persistent GTD, and there are many effective drug schedules. The type, dose, and frequency of the single-agent regimens vary by institution. The reported frequency of primary remission is generally over 60 %, but varies widely, most likely due to differences in criteria for eligibility of single-agent chemotherapy, patient characteristics, dosage and frequency of drug administration, and risk of treatment resistance [55]. In low-risk GTN, some studies suggest that MTX given daily for 5 days every other week is the most effective protocol [56–58].

MTX with folinic acid rescue is well tolerated and has been associated with low toxicity rates [59, 60]. MTX is the preferred regimen in most institutions and has less alopecia/dermatologic toxicity, nausea, and neutropenia compared with actinomycin D [61]. Actinomycin D also produces local tissue damage in case of extravasation. Long-term toxicity data shows that MTX chemotherapy does not increase the risk of secondary tumors; it is unclear whether this is also true for actinomycin D [62]. In addition, MTX can be administered more easily on an outpatient basis (intramuscularly), whereas actinomycin D can only be administered intravenously, and daycase attendance is required.

Most outcome data comparing MTX and actinomycin D come from nonrandomized retrospective studies. Five randomized clinical trials have been performed with varying treatment schemes [61, 63–66]; however, the only sufficiently powered study was a phase III randomized controlled trial of 216 patients, performed by the US Gynecologic Oncology Group (GOG), which compared single-agent MTX chemotherapy (weekly, 30 mg/m^2) to pulsed intravenous actinomycin D (biweekly, 1.25 mg/m^2). In this study, actinomycin D was associated with higher primary remission rates (70 % vs. 53 % for weekly MTX) [61]. While the higher levels of chemotherapy resistance and number of courses required in the MTX treatment arm of the GOG trial might be due to the relatively low dose of MTX used, a higher primary remission rate for pulsed actinomycin D versus weekly MTX was also reported in a meta-analysis that included the GOG study as well as two underpowered randomized controlled trials by Alazzam et al. and Gilani and Yarandi et al. [55, 61]. These studies compared 5-day MTX versus pulsed actinomycin D and 8-day MTX versus 5-day actinomycin D and found that actinomycin D therapy had a statistically significant superior primary remission rate [55, 65].

Since almost all patients treated with MTX or actinomycin D monotherapy are eventually cured, with low associated toxicity rates and preservation of fertility, the results of further research will likely not change daily practice. The use of single-agent MTX will continue, primarily because

actinomycin D is associated with slightly higher levels of toxicity. The optimal number of consolidation courses after achieving normal serum HCG levels also remains to be determined [55, 60, 67]. Currently, treatment with multiday MTX versus biweekly actinomycin D is compared in an international randomized phase III study. This trial (GOG 275, ClinicalTrials.gov identifier NCT01535053) will examine response rates and quality of life of patients receiving multiday methotrexate versus pulsed actinomycin D.

Can We Predict Resistance to Single-Agent Chemotherapy in Patients with Low-Risk Persistent GTD?

Approximately 17–36 % of patients with low-risk persistent GTD treated primarily with single-agent MTX chemotherapy develop drug-resistant disease [53, 59, 60, 68]. These patients have a poor prognosis compared with patients who have relapsed GTN but no treatment resistance [69]. Resistant disease is indicated by a plateau or rise in HCG levels during single-agent chemotherapy. Unfortunately, there are no generally accepted criteria for defining treatment-resistant GTD.

Two studies led to the development of a nomogram for HCG regression during single-agent chemotherapy [70, 71]. Van Trommel and colleagues also developed a serum HCG regression curve based on 79 low-risk patients who were cured and 29 low-risk patients who had failed single-agent therapy with MTX. Using this tool, drug resistance could have been predicted for half of the 29 patients with drug-resistant disease, prior to undergoing a fourth course of MTX, with a specificity of 97.5 % [72]. Although these results were promising, the number of patients in the study was too low to justify the integration of this method in routine clinical practice. An external validation study was later performed at the Charing Cross Hospital, which identified an HCG cutoff value of 737 IU/L that could predict MTX resistance in 52 % of patients at 97.5 % specificity prior to the fourth course of treatment [73]. The use of the HCG cutoff value to assess resistance in the first 3 courses of treatment would have reduced MTX treatment by an average of 2.5 courses. It should be noted, however, that the HCG cutoff values were based on the Charing Cross radioimmunoassay HCG assay, which is not directly comparable to the HCG values obtained by Van Trommel et al. using their HCG assay. An exponential equation for normal HCG regression was developed to circumvent the problem of noncomparable HCG assays [74]. Regardless of the assay used, for patients with HCG levels that do not exceed the cutoff point, a rise or plateau of HCG levels should be included as one of the criteria to identify treatment-resistant disease. Reliable and early detection of treatment-resistant disease permits initiation of the most appropriate therapy as soon as possible, while the patients are still at low risk and the disease is at a curable stage. Conversely, identifying treatment-resistant disease can avoid unnecessarily prolonged exposure to chemotherapy and its adverse side effects.

On the other hand, although the use of a nomogram for HCG regression during single-agent chemotherapy is a promising tool to achieve an adequate chemotherapeutic regimen at an earlier stage, it is important to keep in mind that a separate nomogram would need to be developed for each HCG assay. Each assay has its own sensitivity, specificity, and cross-reactivity, and absolute HCG levels and cutoff points are not comparable. This will be hard to achieve in countries with no centralized management of persistent GTD, where different institutions use different assays. Also, HCG cutoff levels must have a specificity that is as high as possible in order to prevent false-positive diagnosis of chemotherapy resistance, which may lead to overtreatment with a multi-agent regimen that can have severe toxicity and induce early menopause.

Thus, it appears that normal HCG regression curves for single-agent chemotherapy are ready for clinical application, provided that an assay-specific nomogram is developed based on sufficient patient numbers and with very high specificity to prevent false-positive results. Regardless of the HCG cutoff value, patients should be started on a different chemotherapeutic regimen if HCG levels rise or plateau during single-agent therapy, or when clinical disease progression is observed. Development of globally accepted criteria for the diagnosis of resistant GTD is warranted.

How Long Should a Woman Wait to Attempt Conception After Completing Chemotherapy for Low-Risk GTN?

Patients who achieve remission with chemotherapy can expect to return to normal reproductive function [75]; one large study from the Charing Cross Hospital found that of women who had tried to become pregnant after completing chemotherapy, only 7 % failed to conceive [76]. Berkowitz and Goldstein summarized the outcomes of 2,657 pregnancies reported in eight studies; they found that 76.7 % resulted in live births [77], and while the frequency of stillbirth was slightly higher, the frequency of congenital malformations was the same as that in the general population. However, for women who become pregnant before the recommended 12-month follow-up period after completion of chemotherapy, the risks of abnormal reproductive outcomes are higher. In one report by Matsui et al. [78], the incidence of spontaneous abortion, stillbirth, and repeat molar pregnancy was higher in women who became pregnant within 6 months of completing chemotherapy (37.5 %) compared with those who conceived after the 12-month follow-up period (10.5 %).

Thus, although reproductive function is intact following chemotherapy for GTN, women should wait until 12 months after completing chemotherapy and have consistently normalized HCG levels.

Is a Second Curettage Useful in Low-Risk Persistent GTD?

While high cure rates and minimal toxicity with single-agent chemotherapy regimens have been achieved for patients with low-risk persistent GTD, interest in second curettage alone as a potential curative treatment for low-risk persistent GTD is increasing. Theoretically, a second curettage might cure or debulk a persistent intrauterine tumor, allow symptom control in case of persistent vaginal bleeding, and provide additional histological information. There is evidence that a second curettage for persistent trophoblastic disease supports spontaneous remission. In a prospective nonrandomized study, 60 % of 282 patients with persistent GTD (based on elevated HCG) who underwent second curettage did not require adjuvant chemotherapy, compared with 38 % (96 out of 251) of patients with persistent GTD (based on histology) who required chemotherapy [79].

These high cure rates contradict the results of a Dutch study in which 85 patients underwent a repeat uterine evacuation (study group) and 209 patients received adjuvant chemotherapy (control group) for low-risk persistent GTD [80]. Only 8 (9.4 %) patients in the second curettage group were cured by curettage alone. Due to the retrospective nature of this study, group selection was biased towards higher risk factors in the control group—fewer patients had an antecedent nonmolar pregnancy and more patients had pulmonary metastases—which might have led to an overestimation of the benefit of a second curettage [80, 81]. The Pezeski et al. and Van Trommel et al. studies are difficult to compare, however, as different criteria for the definition of persistent GTD and indications for repeat uterine evacuation were used. The criterion used for diagnosis of persistent GTD in Pezeski et al. was rising serum HCG levels or failure of HCG normalization within 4–6-week post-evacuation with or without clinical abnormalities, which differs from the FIGO criteria (Table 26.3) used by Van Trommel et al. [82]. Therefore, with a lower threshold for diagnosing persistent GTD, cure rates in Pezeski et al. were biased towards a better outcome for those undergoing a second curettage.

What is known is that repeat uterine evacuation is associated with a higher risk of uterine perforation, hemorrhage, and infection and should only be performed if there is clear evidence of residual intrauterine trophoblastic tissue. A multicenter phase II randomized controlled trial of second curettage in patients with persistent, low-risk nonmetastatic GTN (GOG-0242, NTC00521118) is currently underway. The results of this trial should be evaluated prior to the routine implementation of a second curettage for low-risk persistent GTD.

Placental Site Trophoblastic Tumor (PSTT)

PSTT can arise from either molar or nonmolar pregnancies and accounts for 0.2 % of all cases of GTD [5]. In contrast to other forms of GTD that arise from villous trophoblast cells, PSTT is generally diploid and is derived from intermediate cytotrophoblast cells. Therefore, PSTT produces lower amounts of HCG relative to tumor volume [83]. By histopathologic examination, PSTT often stains for human placental lactogen [2]. PSTT is slow growing and dissemination usually occurs late by local invasion and lymphatic spread. PSTT may disseminate to distant sites, such as the lung, vagina, other pelvic organs, brain, and retroperitoneum. In most cases, PSTT presents years after causative pregnancy with local symptoms, such as vaginal blood loss [83]. Patients may present with hyperprolactemia due to overproduction by cytotrophoblast cells, in addition to galactorrhea and/or amenorrhea. An elevated free HCG β-subunit to total HCG ratio has been suggested as a way to differentiate PSTT from other forms of GTD [84], although another study revealed that while the HCG-β to HCG ratio may be helpful, it is not specific for PSTT, as this ratio may also be elevated in CCA.

Management of Nonmetastatic PSTT

PSTT is not included in the FIGO 2000 prognostic scoring system; however, survival is approximately 100 % for patients with PSTT localized to the uterus, making this the relatively low-risk subgroup of PSTT patients. Hysterectomy with lymph node dissection is the treatment of choice. Compared to other forms of GTN, PSTT is relatively resistant to chemotherapy and is associated with a high risk of lymphatic spread. Some studies have suggested that chemotherapy may benefit patients with poor prognostic factors, such as a long interval from last known pregnancy, deep myometrial invasion, necrosis, and high mitotic count [85–87]. Due to the extremely low incidence of PSTT, however, chemotherapy regimens are based only on expert opinions, small retrospective studies, and case–control studies. A regimen containing etoposide, MTX, and actinomycin D alternated with etoposide and paclitaxel has been used most frequently [26, 83, 85–87]. The role of radiotherapy for PSTT remains unclear. Because PSTT is slow growing, lifelong follow-up of serum HCG levels is advisable; however, because PSTT produces low levels of HCG, MRI of the pelvis might be helpful to confirm sustained remission [88].

Summary and Future Directions

- Low-risk postmolar GTD is curable with either MTX or actinomycin D. An ongoing trial will compare advantages of one agent over the other.
- Gestational trophoblastic disease is uncommon and there are still many areas where management is controversial.
- Centralization of management by expert centers, experienced in managing gestational trophoblastic diseases, has improved outcome.

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Should Every Woman with Gynecologic Cancer Undergo Routine Screening for Psychological Distress and Sexual Dysfunction?

27

Lesley Stafford and Brigitte Miller

Summary Points

- Arguments in support of routine screening for psychological distress are that distress occurs commonly and can be treated, untreated distress is associated with multiple poor outcomes, distress is often overlooked by oncology professionals, and validated screening instruments are readily available.
- Arguments against routine screening for psychological distress are that screening is inefficient for improving patient well-being, there is no systematic evidence to support the benefit of screening, and the potential harms of universal screening have not been well considered.
- Arguments in support of routine screening for sexual dysfunction are that many women report sexual dysfunction, few women have their communication needs met, and treatment options are available.
- Arguments against routine screening for sexual dysfunction are that more research is needed regarding screening instruments that are easy to use in clinical practice, that many women do not rank the problem as a priority, that attention to local factors often resolves sexual complaints, and problems often resolve after treatment completion.

Psychological Distress

Introduction

There is growing recognition among professional and governmental organizations that psychosocial care is an integral component of the comprehensive care of people diagnosed with cancer. A National Institutes of Health Consensus Conference Statement [1] and an Institute of Medicine report [2] have identified the management of distress and psychiatric disorders among cancer patients as a priority. As the initial step in providing appropriate psychosocial and mental health care, it has been recommended that programs be implemented to provide routine screening for psychological distress among oncology patients [3–5]. For instance, the National Comprehensive Cancer Network (NCCN) have published guidelines recommending that all patients be screened for distress at their initial visit and at regular intervals or when clinically indicated [3].

Despite the strong sentiment in favor of routine screening, it has been argued that there is little empirical evidence that screening results in reduced distress and, increasingly, questions are being raised about the pragmatism and efficiency of such programs [6–10]. One author who has written extensively on the topic says "proponents of screening often do not cite evidence, misquote null findings as supportive, or cite post hoc secondary and subgroup analyses as though they carry the same weight as primary outcomes" [7]. Some criticism relates more specifically to screening for depression and other criticism is inclusive of all forms of distress screening.

In the first section of this chapter, we set out the arguments in support of and against universal screening for distress in cancer care. Distress, as defined by the NCCN Distress Management Panel, is "a multi-determined unpleasant emotional experience of a psychological (cognitive, behavioural, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability,

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sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation and spiritual crisis" [3]. Generally, the data presented here are not specific to women with gynecologic cancer because such data are lacking; however, since the controversy is a methodological one, the arguments made are applicable across tumor streams. In keeping with the NCCN definition above, we have included depression in our discussion on distress.

Argument in Support of Routine Screening for Distress

The rationale for implementation of routine screening for distress among cancer patients rests on several arguments. First, distress occurs commonly. Second, distress is treatable. Third, untreated distress is associated with poor medical, psychosocial, and economic outcomes. Fourth, and most significantly, distress is often overlooked by oncology professionals. Finally, validated instruments are readily available. Each of these arguments is considered below in greater detail.

Prevalence of Distress Is High

The basis of the argument for implementation of routine screening for distress among cancer patients is the high rate of distress associated with cancer diagnosis and treatment. Large-scale prevalence studies have reported rates of elevated distress in excess of 30 % [11–14] with 35–40 % of gynecologic cancer patients reporting heightened distress [11, 12, 14]. An American study of 4,496 patients reported an overall prevalence rate of distress of 35.1 %, with a rate of 29.6 % among the 216 (4.8 %) women with gynecologic cancer [12]. A Canadian study of 2,776 cancer patients reported that 37.8 % of patients met criteria for significant distress [11]. The rate of distress among the 185 (6.7 %) women with gynecologic cancer was 38.3 %. Relative to patients with lymphoma, lung, pancreatic, brain, and head and neck cancers, women with gynecologic cancer had lower levels of distress.

Distress Is Treatable

It is also well documented that psychological distress is often treatable. Randomized controlled trials have demonstrated that a range of psychosocial interventions is effective in improving quality of life and treating cancer-related distress including anxiety and depression [5, 15–17]. While evidence for the benefits of psychological interventions among women with gynecologic cancer is limited by methodological shortcomings and, in some instances, is not very compelling [18], there is some evidence that cognitive behavior therapy [19, 20] and counseling [21] interventions can successfully reduce symptoms of anxiety and depression.

Distress Is Associated with Worse Outcomes

Elevated psychological distress may have a detrimental effect across a wide range of outcomes. Depression, in particular, has a strong, independent effect on many mental health domains and somatic symptom burden in cancer patients, especially when associated with anxiety [22]. Depression has been associated with shorter survival in oncology patients [23], an association potentially mediated by poorer adherence to anticancer treatments [24]. In a large meta-analysis [25], a 25 % higher mortality rate for patients with depression and a 39 % higher mortality rate for patients with major depression were reported even after adjusting for prognostic factors. Patients with depression may also express a desire for a hastened death [26]. Distressed patients exhibit poorer adherence to treatment recommendations [27, 28], possibly because anxiety and depression impair the cognitive focus, energy, and motivation that might be needed to follow through with treatment [29]. Distressed patients are less satisfied with their cancer care [30, 31] and report worse quality of life [32–34]. Finally, elevated distress is associated with increased health service utilization and greater overall healthcare costs [34, 35].

Distress Is Often Overlooked by Oncology Professionals

Despite the high prevalence of distress and the availability of effective treatments to alleviate such distress, oncology professionals' ability to reliably detect psychological morbidity is poor and distress, commonly goes untreated [14, 36, 37]. Compelling evidence of the poor concordance between patients' self-report and oncologists' clinical impression was provided in a large study that investigated the ability of 143 doctors to establish the psychological status of 2,297 patients during outpatient consultations in 34 cancer centers across the United Kingdom [14]. Compared to the results of a validated screening inventory, the doctors' true positive rate was only 29 %, their true negative rate was 85 %, and the misclassification rate was 35 %. Thus, an incorrect assessment of psychological status was likely to have been made for 797 patients.

Unfortunately, though communication training interventions for oncologists have yielded improvements in communication skills and increased knowledge and confidence, detection rates of patient distress have failed to improve [38, 39]. This is likely as a result of multiple considerations. Even if in possession of appropriate communication skills, these may not be utilized in stressful [40, 41], under-resourced clinical environments.

Recognition of psychological morbidity during ordinary consultation may often be hampered by the unwillingness of patients to disclose emotional problems. Despite improvements in public perception, there is still considerable stigma associated with psychological illness [42] and patients may

fear being considered weak. Often there is strongly held belief that a positive attitude or "fighting spirit" is important to either the health outcome or the clinician's willingness to treat the cancer aggressively. Furthermore, patients sometimes are reluctant to disclose their psychological concerns spontaneously, leaving the initiative of discussing these topics to their physician while the physician relies similarly on the patient [43]. Patients, family members, and healthcare providers may believe that feeling depressed or hopeless is a normal and inevitable part of living with cancer. This attitude discourages disclosure by patients and appropriate clinical management by clinicians.

Another consideration as to why distress may not recognized by oncologists is its clinical presentation. Detection of distress, particularly a standard criteria-based syndrome of major depression, is often confounded in cancer patients because the neurovegetative features of depression such as sleep disturbance, psychomotor retardation, appetite disturbance, poor concentration, and low energy may also be attributable to symptoms of cancer or treatment side effects. Somatic complaints and those of general malaise, fatigue, and lethargy are also more frequent among older patients with depression, rendering the diagnosis more difficult [44]. This is confirmed by the finding that older patients with cancer are much less likely to be diagnosed with depression in comparison to younger patients in whom affective complaints are more frequent [45].

In addition to older patients with cancer, another population vulnerable to underdiagnosis and treatment of depression is the socially disadvantaged. In one study of low-income women with cancer, depression was diagnosed in 30 % of breast cancer patients and in 17 % of gynecologic cancer patients, but only 12 % of women who met criteria for major depression were on antidepressant medication and only 5 % were seen by a counselor [46]. In contrast, 80 % of college-educated women with cancer and depression were noted to receive medication [47]. Thus, routine screening would ensure more equitable access to psychosocial and mental health support than reliance on physician recognition.

Validated Instruments Are Available

Clearly, reliance on patient-initiated or oncologist-determined referral to psychosocial services is likely to overlook and/or fail to identify a substantial proportion of distressed patients requiring assistance. In mental health, the gold standard to assess emotional distress is a comprehensive interview typically conducted by a clinical psychologist or psychiatrist. The expense and time involved in such traditional mental health assessment is prohibitive in an oncology setting in which every patient is to be assessed for distress. The solution lies in the use of brief, validated self-report questionnaires. Patients may feel more comfortable revealing sensitive information during the completion of a questionnaire than in person.

A wide range of high-quality, well-validated generic and cancer-specific screening instruments is available [48]. Recommended instruments include the two-item combination depression question, the Center for Epidemiologic Studies Depression Scale, the Hospital Anxiety and Depression Scale, the Beck Depression Inventory, and the General Health Questionnaire-28 [48]. A discussion of the merits and psychometric properties of the various measures is beyond the scope of this chapter, but the interested reader is referred to two recent systematic reviews detailing the diagnostic accuracy of instruments for detecting both distress [48] and depression [49] in cancer settings.

Summary

In summary, proponents of universal screening for distress among women with gynecologic cancer note the high prevalence of distress among these women and the often successful treatment of such distress, if detected. Conversely, failure to identify distress may result in detrimental effects across a range of important outcomes. Perhaps the most compelling argument for routine distress screening is that patient-initiated or oncologist-determined detection of distress is highly unreliable and the distress of many patients goes unrecognized. Fortunately, several psychometrically sound, inexpensive screening instruments are available for use in routine oncology care. The use of such instruments to rapidly and prospectively identify those patients who are struggling with the challenges of cancer diagnosis and treatment promotes equitable access to psychosocial and mental health care, avoids potential crises by promoting early identification, and reduces stigma often associated with distress.

Argument Against Routine Screening for Distress

The argument against universal screening for distress is simple. Firstly, there are few data on the practical utility of screening, but existing data do show that screening is an inefficient method of improving the well-being of individuals with cancer. Secondly, there is a clear absence of systematic evidence to demonstrate the benefit of either screening specifically for depression or screening for general psychosocial distress in patients with cancer. Thirdly, the potential harms of universal screening have not been well considered. These arguments are considered in more detail below.

Screening for Distress Is Not Efficient

To demonstrate the argument that universal screening for distress is not as efficient as one might like, it is useful to consider the definition of screening offered by the United Kingdom National Screening Committee [7]. Screening is defined as "a public health service in which members of a

defined population, who do not necessarily perceive they are at risk of, or are affected by, a disease or its complications, are asked a question or offered a test to identify those individuals who are more likely to be helped than harmed by future tests or treatment to reduce the risk of disease or its complications" (p.6). In theory then, in the context of the current debate, screening seeks to detect distress, including depression, that would not otherwise be detected and treated [9]. In practice, however, existing studies of the validity and yield of screening tools in cancer settings are limited by the inclusion of all available patients, including those who have already been recognized and are being treated for psychological disorder [6]. This inclusion serves to inflate the estimates of the number of patients in need of treatment that screening can yield. In a recent systematic review of the diagnostic accuracy of screening tools for depression [50], only 8 of 197 reports from 17 systematic reviews and meta-analyses were found to specifically exclude patients already diagnosed with or being treated for depression. This inflation effect was demonstrated in a recent study of 437 newly diagnosed breast cancer patients [6]. Patients received in-clinic distress screening and telephone-based psychiatric interviews. Although 39 % of patients with elevated distress had a psychiatric disorder, the positive predictive value of screening fell to 15 % for an untreated psychiatric disorder. Only 6 % had untreated depression. Thus, the proportion of patients with unidentified and untreated morbidity was considerably less than the proportion of those who were receiving treatment but remaining symptomatic (approximately two-thirds).

Patients with a psychiatric disorder like depression who are already receiving treatment may differ from those who are not by having a more pronounced disorder or a more positive attitude to treatment [51, 52]. As demonstrated by a study that involved screening "high-risk" medical patients [53], there may also be challenges to engaging patients with untreated depression in appropriate treatment. Of the 1,687 patients invited for screening, 71 were identified as having major depression, and 36 of these were already in treatment. Of the remaining 35 patients, 14 refused treatment and 4 did not attend the appointments. Ultimately, in order for one previously unidentified depressed patient to receive treatment, 118 patients had to be invited for screening. Consequently, it has been argued [6] that patients reliant on screening to detect psychological morbidity may be more difficult to diagnose and require additional resources to overcome resistance to treatment, whereas those patients already receiving treatment but with enough residual symptoms to screen positive may require improved surveillance and greater coordination of care with outside providers.

Thus, the role of screening as a means of identifying patients with untreated psychological illness is doubtful. Screening might be more appropriately utilized as the first step in monitoring the effectiveness of ongoing treatment (as suggested above) [54] or as a prompt for improving communication surrounding psychosocial issues. Indeed, it has been reported [10] that the majority of professionals involved in 14 Dutch implementation projects of routine screening among cancer patients cited their main reasons for implementing screening as an aid to communicating with patients and providing systematic care.

The motive of facilitating psychosocial referral for distressed patients does not translate easily in practice. Existing data show that the desire for psychosocial support may not be correlated with distress levels and many patients with low levels of distress who score below the cutoff criterion on a screening tool may want psychological support [55–57]. In one study of breast cancer patients [58], a third of women had moderate to severe anxiety or depression on screening, but only 58 % of these accepted referral to counseling. Importantly, 45 % of those who fell below the cutoff criterion were interested in and did receive counseling. Counseling was offered to all patients with moderate to severe distress and those expressing a wish for support. Stated differently, of those who actually received counseling, only 38 % would have been referred on the basis of screening outcome, but 71 % would have been referred on the basis of questioning the patient's interest in receiving supportive counseling. These data suggest that a screening program could be dispensed with and, instead, patients could simply be asked if they would like a referral for psychosocial support [7, 10].

If the desire for help is not necessarily associated with distress, screening programs may need to have a broader focus, and perhaps include identification and addressing of unmet needs [59]. Data from women previously diagnosed with gynecologic cancer show that 87 % have at least one unmet need and 25–30 % have an unmet need for assistance with worry about cancer recurrence, reducing stress in their lives or concerns about communication in the healthcare team [60]. It would be unacceptable to deny these individuals access to psychological help on the basis of suffering from serious adjustment problems rather than a psychiatric disorder [10].

A final comment on the potential inefficiency of routine screening relates to the resources required for a successful program. Screening is best construed as an initial step in a process in which positive screens are followed up by clinical interviews to determine diagnosis and treatment [61]. These interviews would require the availability of suitably qualified mental health staff, usually clinical psychologists or psychiatrists. While the prevalence of major depression in cancer patients is higher (approximately 11 %) than in the general population (approximately 5–6 %) [62], the modest prevalence of psychiatric disorders in most cancer populations would mean that most positive screens are false positives rendering screening potentially inefficient [54].

Lack of Systematic Evidence Demonstrating Benefits of Screening

Perhaps the most compelling argument against routine screening is the absence of systematic evidence to demonstrate the benefit of either screening for distress or for depression specifically in patients with cancer. Bidstrup et al. [8] reviewed randomized controlled trials of the effect of screening for psychological distress on psychological well-being among cancer patients where distress was taken to include depression, anxiety, anger, and quality of life. Among the 7 identified trials, only 3 showed an effect on psychological outcome [56, 63, 64], 1 showed an effect only among those patients depressed at baseline [65], and there was no significant effect in the remaining 3 studies [66–68]. Unfortunately, these trials generally included poor documentation of the interventions that followed the screening, so that any lack of effect might have been due either to failure of screening or to lack of an effect of a subsequent psychosocial intervention. None of these studies comprised women with gynecologic cancer. Only limited conclusions can be drawn from this review due to the heterogeneous intervention content, outcome measures, and design of the seven studies, but the authors concluded that it is premature to declare that psychological screening improves the well-being of cancer patients.

Meijer et al. [49] systematically evaluated the potential benefits of depression screening in cancer patients. The main finding of the review was that there are no randomized controlled trials that have evaluated whether screening for depression among cancer patients would improve depression outcomes. The authors also reviewed the performance of depression screening tools. They reported 19 studies of screening accuracy, most of which used exploratory methods to identify cutoffs that would maximize diagnostic validity in a specific sample. It was noted that these methods tend to inflate estimates of screening accuracy and do not replicate consistently in other samples. Samples were also small with a median size of 17 depression cases samples and comprised patients with breast cancer or mixed diagnoses. The results of their review do not support the recommendation to screen patients for depression as a standard part of supportive oncology care.

Potential Harm from Screening for Distress

In the absence of empirically demonstrated benefit, any potential harm arising from psychosocial screening should be carefully considered. If routine screening is promoted on the basis of ensuring equitable access to psychosocial care, then attention must be paid to those patient groups who would have difficulty with self-report scales, for example, those with visual, cognitive, or language impairment or fatigue. Similarly, cultural and language barriers also require thought.

It is possible that routine screening for distress might lead to inappropriate labeling and treatment. Implementation of ultrashort screening instruments, in particular, with their poor accuracy for confirming the presence of elevated distress, is likely to result in many patients who are not distressed receiving inappropriate referrals [61]. This would represent an impractical use of the typically scarce resources available for psychosocial care. Mislabeling of some patients as distressed may also have the unintended consequence of causing distress where it was not previously present [69].

Certainly, routine screening for depression could increase the number of cancer patients diagnosed with depression and treated with antidepressant medication [47, 70], thereby exposing more patients to potentially dangerous drug interactions between antidepressants and either chemotherapeutic or antiemetic agents [70–72]. Interactions between anticancer drugs and antidepressants are of particular concern because small alterations in the plasma concentrations of certain members of either drug class can lead to either subtherapeutic effects or drug toxicity [71].

Summary

Data on the practical utility of screening are sparse, but existing data suggest that screening is potentially inefficient. In relation to screening for psychosocial distress, it is still too early to conclude whether screening improves the psychological well-being of cancer patients. In relation to screening for depression, there is currently no systematic evidence to support recommendations for universal screening in cancer care. Stronger, high-level evidence demonstrating that routine screening results in better outcomes is needed before such programs will or should be broadly adopted. Potential harm from screening has also not been fully considered.

Conclusion and Recommendations

The high prevalence of distress among individuals with cancer, including women with gynecologic cancer, is well established and undisputed. Similarly, there is widespread agreement on the value of appropriate management of psychosocial distress to minimize the overall burden of disease. Unfortunately, the state of the science in terms of identifying distress and developing practice guidelines has outpaced both the capacity of the average oncology unit to deliver services as optimally recommended as well as the empirical evidence needed to justify these services. Both proponents and critics of the widely advocated initiative to implement universal screening recognize that the need for psychological care and access to such care is far from uniform. Critics, however, point out that screening for distress, including depression, is only useful in so far as it leads to improved outcomes above and beyond existing care. While dozens of studies have investigated the psychometric properties of various screening tools and large amounts of scarce resource are

being devoted to implementation of routine screening programs, the efficiency and practical utility of such programs have not been proven. By extension, there are no data specific to women with gynecologic cancer.

Suggestions as to how to improve on the status quo are varied. Some have suggested that screening should be dispensed with and that patients should simply be offered the opportunity to discuss their psychosocial concerns [7, 10]. The resources and staff that would have been deployed for screening could be used for improving staff-patient communication. Such an approach would ensure that patients have access to psychological support regardless of whether they exceed the threshold on an instrument. For this approach to be successful, attention would need to be paid to increasing staff confidence and effectiveness in supporting distressed patients.

Alternatively, it has been suggested that the population of patients screened be altered to focus on those who are considered to be at high risk or otherwise identified by physicians as distressed [8, 59]. Targeted screening is more efficient than systematic screening because the prevalence of morbidity is higher. Moreover, psychosocial treatment among cancer patients is often more successful when the baseline severity of the condition is high [73]. Targeted screening can, however, miss many patients thought to be at low risk; so the first step in identifying who is at high risk is a screening tool with a high negative predictive value [8].

A related suggestion, particularly when screening is focused on detection of psychiatric illness like depression, is to use screening to monitor the clinical response of patients already identified as depressed and receiving treatment, relying on this information to improve the quality of care [59]. Both this approach and the one suggested above are reactions to concerns that ineffective screening may divert scarce resources from more seriously depressed patients who may receive inadequate treatment as a result [9]. Oncology clinicians would need additional resources to manage psychiatric care in these settings in addition to being willing to intervene in existing treatment relations with other external providers.

Ultimately, to answer the question about whether every woman with gynecologic cancer should be routinely screened for distress, well-designed and executed randomized controlled trials evaluating the merits of such programs are required. In such trials, all patients identified as distressed via screening or by physician recognition and referral and those in a control group should have access to high-quality, integrated psychosocial care. The effect of excluding diagnosed or currently treated patients on screening performance must be considered. Future studies should take into account measurement of unmet needs [59], desire for help, clinical responses, and longitudinal outcomes [8]. Distress must be included as a patient outcome; a detailed, theory-based distress management plan must be described; staff training offered; and staff and patient use of any subsequent interventions tracked [8]. A distress management plan is important to ensure that staff systematically act on screening results; it also implies that the healthcare system has the requisite resources for handling distress. Lack of training might mean that staff do not know how to follow-up screening results and consequently do not always use them [64, 66]. Large surveys of oncology professionals have found that barriers to poor uptake of screening tools are time, insufficient training, low confidence [74], and poor availability of mental health services and knowledge about screening guidelines [75].

In conclusion and based on the data presented here, the usefulness of universal distress screening has not yet been demonstrated. Stronger, high-level evidence showing that routine screening for distress results in better outcomes is needed before such programs will or should be broadly adopted.

Sexual Dysfunction

Introduction

It should be no surprise that treatment for gynecologic malignancy has the potential to change sexual function significantly. Using a Web-based survivorship tool to collect toxicity data from 390 survivors, change in sexual function was mentioned by 51 % of the patients [76]. Surgery and radiation therapy affect the area of sexual function directly as well as the hormonal status, and chemotherapy often leads to menopause and related profound effects on sexual function. Unless surgery is very radical, the long-term effects of radiation therapy seem to be more important compared to the effects of surgery. In addition, emotional problems related to a decrease in performance status, change in body image, change in interpersonal relations due to prolonged illness, and the necessity of dealing with a life-threatening disease process among others will have an impact. There are quite a number of studies evaluating the effect of cancer diagnosis and treatment on sexuality, but many studies include only a small number of patients diagnosed in different stages and treated differently so that a more detailed analysis is often not possible. In addition, the instruments used for evaluation are not always validated and cutoff points vary. This explains some of the discrepancies between reports. Different effects can be expected related to the type of cancer due to the most frequent treatments used and the average age of diagnosis. Most reports focus on treatment-related local factors and do not include the emotional and social components. Lastly, only few reports are available describing therapeutic interventions. For all these reasons, many recommendations are based more on opinions than on well-proven data.

Arguments in Favor of Routine Screening for Sexual Dysfunction

Many Patients Have Problems

Sexual function after treatment for a gynecologic malignancy can be impaired in many different ways depending on types of treatment, diagnosis, and age, among other factors. Most studies so far have focused on the physical aspects such as vaginal function, dyspareunia, and hormone status with its effects on vaginal tissues and libido. In addition, significant changes have been noted regarding the psychosocial aspects of sexuality [77]. Effects of treatment are seen many years after completion. In-depth interviews with cancer survivors revealed that physical symptoms may lead to sexual difficulties after a period of time [78]. Evaluating patients 1–5 years after completion of treatment for cervical cancer, Donovan noted that time since treatment, radiation therapy, partner relations, perceived physical appearance, and vaginal function accounted for about 50 % of the variance in sexual health in comparison to healthy women matched for age and education [79]. These findings support the fact that the impact of cancer treatment goes far beyond the effect on vaginal function and that treatment of the vaginal issues alone, while important, will not resolve all sexual problems. Social factors play an important role as well, for example, the development of decreased sexual function is more frequent among Hispanic women compared to non-Hispanic white women [80].

A diverse range of problems is seen after treatment for cervical cancer. Radical hysterectomy was shown to decrease all aspects of sexual function. Although postoperative recovery is faster after laparoscopy, sexual function is impaired as well after these procedures because the pelvic dissection is similar. The shortening of the vagina can be compensated in most cases, but the effects of pelvic nerve- and blood supply seem to play a more important role [81]. This confirms the findings of an earlier observational, longitudinal study evaluating micturition, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer [82].

The shortening of the vagina after radical hysterectomy rarely causes significant problems, but dyspareunia may develop due to scarring and adhesions in the pelvis. On the other hand, radiation therapy leads to loss of ovarian function and firmness and sometimes scarring of the vaginal tissues, resulting in a significant decrease in lubrication. A literature survey evaluating 23 studies, although only eight were reported to have a good methodology, revealed that the effect of hysterectomy on sexual function is much less compared to radiation therapy [83].

The impact of surgery for early endometrial cancer seems to be low and outcomes regarding sexual function are similar to those seen after hysterectomy for benign reasons [84]. This finding has been disputed in another publication. Here again, most patients were diagnosed in early disease and treated with surgery only, but in this report 89 % of patients were diagnosed with sexual dysfunction with an FSFI (Female Sexual Function Index) score below 26. It is not clear that treatment is the only variable explaining the results. Although histologic grade correlated significantly with the FSFI status, the same was found regarding relationship status, self-reported mental health, and diabetes [85]. The main impact for endometrial cancer patients seems to originate from the hysterectomy. The effect of brachytherapy seems minimal [86]. Quality of life assessments after completion of treatment in the PORTEC-2 study revealed no significant differences between external beam radiation therapy and vaginal brachytherapy regarding sexual function; however, increased complaints of vaginal dryness and decreased levels of sexual enjoyment were reported when compared to the normal population [87]. There are no data regarding the effect of pelvic radiation in combination with chemotherapy in patients with endometrial cancer because these treatment options are used less frequently.

Lack of interest in 36 % and physical problems described by 23 % were the most frequent aspects of decreased sexual function in ovarian cancer patients. Also, there are a considerable number of confounding factors such as premenopausal bilateral salpingo-oophorectomy leading to surgical menopause, age, chemotherapy, mental health factors, and body image, all of which were significantly related to sexual function on multivariate analysis [88]. Similar results were found in patients after conservative surgery and chemotherapy for ovarian germ cell tumors. After a minimum follow-up of 2 years, patients reported less sexual pleasure and lower scores regarding total sexual activity when compared to healthy control groups. On the other hand, relationships with partners tended to be stronger and more positive [89]. In addition, the extent of chemotherapy is important. Patients during first-line treatment for ovarian cancer have less problems compared to patients undergoing treatment for recurrent disease. Again, many confounding factors will impact this result [90].

Due to the extensive scarring and occasional resection of the entire clitoris, the effect of radical vulvar surgery on sexual function is profound. However, it should also be noted that even resections for preinvasive disease, especially if extensive and if done on several occasions, can have a significant impact [91].

Communication Needs Are Not Addressed

Although most patients are satisfied with their cancer care, Lindau noted in 2007 that this does not hold true for services received for sexual health [92]. Some patients feel uncomfortable talking about sexual function or initiating such a conversation. Therefore, this study among

long-term survivors of cervical cancer in the United States revealed that 74 % would appreciate if the physician would ask about sexual issues. Most of the survivors, 63 %, noted that they had never had a conversation regarding sexual function before, during, or after treatment. It is important to mention that the average age at time of cancer diagnosis in this study was about 22 years and that patients were interviewed an average of 27 years after the treatment. The importance of these issues decreases with increasing age but remains important for many patients [93]. Most physicians assume that there are significant sexual problems among their patients; however, many physicians also do not feel comfortable talking about sexual function due to lack of time, lack of training, and embarrassment [94].

Treatment Options Are Available

There certainly is a desire for treatment from the patient's point of view. A recent study revealed that 41 % among gynecologic and breast cancer survivors, median age 55 years, are interested in receiving care regarding sexual heath, but only 7 % had actually sought medical help; 30 % stated that they would see a physician to address such matters. The need was reported higher among younger patients [95].

Treatments have focused on local factors such as lubrication and vaginal dilatation as well as hormonal factors by using estrogen replacement therapy. In patients after radiation therapy for cervical cancer, a clitoral therapy device was noted to be beneficial for improving vaginal function, desire, arousal, and orgasm. Improvements were monitored with validated instruments such as the FSFI and the Derogatis Interview for sexual functioning. After 3 months of treatment most patients reached low normal levels [96]. General acceptance of this device, however, was low and trials using other instruments are still ongoing.

Few studies are available investigating the effect of psychological interventions although there is moderate evidence for feasibility and effectiveness. Focused counseling may significantly improve sexual relationships [97].

Summary

Sexual dysfunction is seen frequently among survivors of gynecologic cancer and may remain significant for many years after completion of treatment. Different aspects have to be taken into considerations for the different malignancies of the gynecologic tract. Physicians and patients do not always feel comfortable talking about these questions, especially not during a short clinic visit with a focus on cancer care. Treatment options are available although much more research is necessary regarding effectiveness.

Arguments Against Routine Screening for Sexual Dysfunction

Not All Patients Rank This Problem High

A study involving young patients in Thailand revealed only a minimal effect of radical hysterectomy on sexual function; however, only 46 % of these patients also had undergone surgical menopause [98]. Frumovitz et al., who evaluated 114 women at least 5 years after completion of treatment, reached a similar conclusion. Sexual function after hysterectomy was similar to that of patients without a history of cancer in both univariate and multivariate analysis [99].

Attention to Local Factors Solves Most Complaints

A variety of options are available to improve vaginal function after cancer treatments including hormonal medication (creams, tablets, rings), lubricants, and moisturizers. Dilator therapy is another option. With attention to detail, a large variety of vaginal symptoms can be resolved or at least significantly improved so that the impact on overall sexual function is decreased [100]. In one study [101] there was no difference in dyspareunia, confirming the results of good local therapy, among survivors free of disease a year or more after treatment for a gynecologic malignancy, but a decrease in sexual desire and a decrease in the ability to climax was noted in comparison to healthy women seeking gynecologic care.

Problems Resolve After Completion of Treatment

A long-term follow-up study including patients with endometrial cancer after surgery allocated to external radiation therapy or observation (PORTEC1) did not reveal significant differences regarding vaginal symptoms or sexual functioning; however, only 24.3 % of the patients reported sexual activity. Patients seen 1 year after radical hysterectomy or chemotherapy were compared to patients who underwent hysterectomy for benign disease. No significant differences were found regarding sexual activity (76 % versus 84 %) and sexual enjoyment. Vaginal function, however, was decreased among the cancer survivors [102]. After radical hysterectomy alone only a slight decrease in sexual function can be expected. Only minimal changes were seen in ten parameters of sexual functioning except for the amount of sexual activity [103] after nerve-sparing radical hysterectomy.

Overall complaints are higher in patients evaluated during the first 2 years of completion of treatment in comparison to patients evaluated later: Frumowitz noted little significant changes in patients evaluated 5 years after treatment, whereas Butler-Manuel reported worse sexual function mentioned by 55 % of 38 women an average of 16 months after treatment, but not more than 25 months.

Thirteen percent reported improved sexual function and 13 % had stopped sexual relations completely [104]. In another study 173 patients were prospectively followed after radical hysterectomy with regular questionnaires every 6 months until 24 months. Results were matched to an age-matched control group from the general population. Most complaints had decreased at the 24 months' mark. Cervical cancer survivors identified dyspareunia in 23 %, decrease in sexual desire in 15 %, and vaginal dryness in 12 % as the three most bothersome symptoms. The effect on overall quality of life was noted as minimal [105]. For young patients undergoing surgical menopause due to risk-reducing BSO, the impact on sexual function is significant during the initial 6 months, but after that time problems resolve in most patients [106].

Summary

There is evidence from the literature that the effect of cancer treatment on sexual function does not play an important role for overall quality of life for many patients, that careful attention to local care can alleviate most problems, and especially that problems resolve over time. The studies evaluating treatment options for sexual dysfunction are small and not always well done. There is no definite proof at this time that treatment will be of significant benefit.

Conclusion and Recommendations

Unfortunately the conclusions reached regarding screening for sexual dysfunction are similar to those reached for psychological distress. Although sexual dysfunction is frequent among survivors of gynecologic malignancies, overall there are far less reports regarding screening compared to screening for distress and depression. Studies are difficult to evaluate due to methodological concerns including small study populations, often short follow-up, few longitudinal evaluations, various instruments used, and focus on just some aspects of sexual function, among others. On the other hand, the reluctance of discussing these issues among patients and physicians appears even greater. The experience regarding treatment is even more limited in the literature. Resource constraints are even worse: in the day-to-day clinic it is possible to take care of local factors, but getting an appointment with a sex therapist is very difficult. Therefore routine formalized screening for sexual dysfunction cannot be recommended at this time. More well-planned research is necessary regarding instruments, impact, and treatment options. Still, even now the physician should take the initiative and at least ask a few questions about sexual function. This is not a perfect solution, but will be helpful to many patients.

Concluding Comments

- The high prevalence of distress among gynecologic cancer patients and the value of appropriate management of this distress are undisputed, but the usefulness of universal distress screening has not yet been demonstrated.
- Stronger, high-level evidence showing that routine screening for distress results in better outcomes is needed before such programs will or should be broadly adopted. In future trials, all patients should have access to high-quality, integrated psychosocial care, and the effect of excluding diagnosed or currently treated patients must be considered. Measurement of unmet needs, desire for help, clinical responses, and longitudinal outcomes must be considered.
- Methodological limitations of existing studies restrict useful evaluations of screening for sexual dysfunction, so routine screening for sexual dysfunction cannot be recommended until further research on suitable instruments, impact on quality of life, and treatment options are conducted.
- Physicians should initiate discussion with patients about sexual function and should pay careful attention to the treatment of local factors in all patients as well as hormonal replacement therapy whenever possible.

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How Should Gynecological Sarcomas Be Managed?

28

Beatrice Seddon and Frederic Amant

Summary Comments

- The role of pelvic lymph node dissection and oophorectomy in uterine leiomyosarcoma.
- The roles of adjuvant chemotherapy and radiotherapy in uterine leiomyosarcoma.
- The role of systematic and targeted therapies in advanced/metastatic uterine leiomyosarcoma.
- The role of oophorectomy in endometrial stromal sarcoma.
- The role of adjuvant hormonal therapy in endometrial stromal sarcoma.

Introduction

The commonest uterine tumors are epithelial in origin, but the uterus also gives rise to mesenchymal tumors arising from endometrial stroma or myometrial smooth muscle. In the USA, uterine sarcomas represent 8 % of all uterine cancers [1], and they constitute 7 % of all soft tissue sarcomas [2]. In Finland, where the cancer registry has good coverage and accuracy on all solid tumors, the estimated incidence of uterine sarcomas is approximately 0.71 per 100,000 women [The Finnish Cancer Registry Available at: http://www.cancerregistry.fi]. Uterine sarcomas include leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), adenosarcoma, and undifferentiated endometrial sarcoma (UES) [3]. More uncommon variants include (embryonal) rhabdomyosarcoma, chondrosarcoma, liposarcoma, and osteosarcoma. Uterine sarcomas can be "low" grade (ESS, adenosarcoma) or "high" grade (uLMS, adenosarcoma with sarcomatous overgrowth, UES). In a Norwegian study that excluded endometrial carcinosarcoma, the most common sarcoma types were uLMS (63 %) and ESS (21 %), whereas UES (6 %) and adenosarcoma (6 %) were uncommon [4].

Uterine carcinosarcomas have historically been classified as a type of uterine sarcoma. However, more recent evidence suggests that these biphasic tumors should be classified as a subtype of endometrial carcinoma, as their tumor biology points toward a single epithelial stem cell origin as shown by in vitro data, immunohistochemical studies, and molecular comparison between the epithelial and mesenchymal component [5, 6]. They are not further discussed here.

Historically, uterine sarcomas were staged as endometrial carcinomas, with no separate classification. Recently, a new staging system for uLMS, ESS, and adenosarcoma has been published by FIGO (International Federation of Gynaecology and Obstetrics) [7, 8] (Table 28.1). Uterine sarcomas usually present with symptoms of abnormal vaginal bleeding, pelvic pain, or abdominal distention [9, 10]. The presenting signs include an enlarging uterus, a mass or polyp visible on speculum examination, and parametrial induration. However, these symptoms and signs are not specific.

In this chapter, we discuss standard treatments and controversies in the management of pure mesenchymal uterine tumors.

Uterine Leiomyosarcoma

Epidemiology and Diagnosis

uLMS represents approximately 1.3 % of uterine malignancies [3] and is the most common uterine sarcoma accounting for approximately 56 % of the total [4]. A recent large population-based study has reported that median age of 1,396 patients with uLMS was 52 years. The majority of patients

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Table 28.1 Staging for uterine sarcomas (leiomyosarcomas, endometrial stromal sarcomas, adenosarcomas)

1. Leiomyosarcomas and endometrial stromal sarcomas		
Stage		**Definition**
I		Tumor limited to uterus
	IA	≤5 cm
	IB	>5 cm
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	>One site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis
2. Adenosarcomas[a]		
Stage		**Definition**
I		Tumor limited to uterus
	IA	Tumor limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to half myometrial invasion
	IC	More than half myometrial invasion
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	>One site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis
3. Carcinosarcomas		
Carcinosarcomas should be staged as carcinomas of the endometrium		

[a]Note: Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors

(68.1 %) presented with FIGO stage I disease, with 3.1, 7.1, and 21.7 % with stages II, III, and IV disease, respectively. Outcomes related to stage of presentation, with 5-year disease-specific survival rates for patients with stage I, II, III, and IV disease of 75.8, 60.1, 44.9, and 28.7 %, respectively [11].

The disease is often initially asymptomatic, and the diagnosis of a sarcoma is frequently missed, because benign pathologies such as uterine leiomyomas and adenomyosis can mimic uLMS [12]. An unusual growth of a fibroid is an indication for uterine resection, as uLMS cannot be excluded. However, it is estimated that the chance of encountering a sarcomatous lesion in these cases is less than 1 %.

A diagnostic biopsy is often not informative because uLMS is most commonly located in the myometrium. Only larger uLMS that grow through the endometrial lining can be diagnosed by endometrial biopsy or curettage, and this adds to the difficulty in diagnosis of early-stage uLMS.

Early diagnosis of uLMS can be problematic, in particular the reliable distinction between malignancy and a degenerating fibroid. However, there are no pathognomonic imaging characteristics for uterine sarcomas [13, 14]. On ultrasound uLMS present as large, ovoid-shaped tumors with an inhomogeneous content due to the tumor tissue and central necrosis, leading to a "bizarre" internal echo pattern. Color Doppler ultrasound showed initial promise [15], but features are nonspecific and there is much overlap with ultrasound features of benign leiomyomas [16]. Computer tomography (CT) scanning is easily accessible in developed countries, but is expensive and not ideal as a screening tool as it utilizes ionizing radiation, and is not able to differentiate between benign leiomyomas and uLMS [17]. Magnetic resonance imaging (MRI) is less accessible and more expensive, but does not use ionizing radiation. However, as with CT, uLMS and leiomyomas show many overlapping features on MRI [18–21]. Use of ^{18}Fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful as uLMS accumulates ^{18}FDG moderately to intensely [22, 23], but once again differentiating from benign pathology can be difficult as

Table 28.2 Hormone receptor expression in uterine sarcomas

Study	*N*	ER positivity (%)	PrR positivity (%)
Leiomyosarcoma			
Sutton et al. [31]	43	56	56
Bodner et al. [32]	21	57	43
Ioffe et al. [29]	13	100	–
O'Cearbhaill et al. [33]	31	71	50
Koivisto-Korander et al. [30]	27	42	56
Leitao et al. [34]	43	42	40
Endometrial stromal sarcoma			
Reich et al. [35]	21	71	95
Chu et al. [36]	10	80	90
Balleine et al. [37]	9	–	100
Zhu et al. [38]	21	48	52
Kurihara et al. [39]	18	94	94
Ioffe et al. [29]	17	76	–
Koivisto-Korander et al. [30]	8	50	50

ER estrogen receptor, *PrR* progesterone receptor

leiomyomas in premenopausal women and adenomyosis can also show pronounced uptake of ^{18}FDG [24, 25].

Thus, while several radiological features may raise suspicion of uLMS, there are no pathognomonic features on any imaging technique. Promising new tests to differentiate between leiomyoma and uLMS include the combined use of MRI and serum lactate dehydrogenase [26] and transcervical needle biopsy [27]. However, these tests have not as yet been validated in prospective studies.

Histopathology

Most uLMS are composed of fascicles of spindle cells with abundant eosinophilic cytoplasm enabling the recognition of their smooth muscle nature, with cellular characteristics of a malignant tumor [3]. The main criteria to diagnose uLMS are the Stanford criteria and include a high mitotic index, presence of atypia, and coagulative tumor cell necrosis [28]. This approach enables distinction between uLMS from mitotically active or atypical leiomyomas and uterine smooth muscle neoplasms with low malignant potential. Coagulative tumor cell necrosis is a hallmark feature, but should be discriminated from hyaline and ulcerative necrosis [28]. uLMS can express hormone receptors, which is linked to a better prognosis [29, 30]. A number of studies have assessed hormone receptor positivity in uLMS, showing rates of 42–100 % for estrogen receptors and 40–56 % for progesterone receptors (Table 28.2).

A small subset of uLMS exhibit a more prolonged natural history, in contrast with the more usual aggressive clinical course associated with uLMS. There is considerable debate on the existence of a "low-grade" uLMS entity, although this subset of uLMS qualifying for the Stanford criteria certainly has a more indolent growth [40]. From a therapeutic view it is important to note that these indolent tumors are more likely to be hormone receptor positive [41].

Early-Stage Disease

What Is the Role for Lymph Node Dissection and Oophorectomy?

Surgery with removal of the uterus by hysterectomy is the cornerstone of management of early-stage uLMS. When the diagnosis of uLMS is known preoperatively, a midline incision that allows full exploration of the peritoneal cavity is preferred. The relative necessity of bilateral salpingo-oophorectomy and lymphadenectomy has been studied. Lymph node involvement is infrequent, only present in approximately 3.5–11.0 % of early-stage uLMS, with higher incidences in advanced-stage disease [11, 42–44]. Similarly, ovarian involvement is unusual (<5 %) and is also a feature of advanced-stage disease [43]. The clinical benefit of both procedures has been studied in a large series of 1,396 patients, in which both oophorectomy and lymphadenectomy failed to be independent prognostic factors for survival [11]. Standard treatment for early-stage uLMS therefore consists of hysterectomy without oophorectomy or lymphadenectomy [45].

As preoperative diagnosis is challenging, patients frequently undergo surgery for presumed fibroids, and therefore a Pfannenstiel incision or an endoscopic approach are common. Uterine fibroids can be removed endoscopically, even when large. Different techniques are used to reduce fibroids to a volume that allows removal, including coring of the uterus, uterine transection, or morcellation. However, this approach is not appropriate for uLMS, and indeed 25 patients undergoing inadvertent morcellation of uLMS had an increased rate of abdominopelvic dissemination. Morcellation also adversely affected disease-free survival and overall survival [46], underscoring the importance of preoperative diagnosis. Thus, if uLMS is suspected, the uterus should be removed intact. This is particularly important when a presumed fibroid does not respond to gonadotrophin-releasing hormone analogue therapy, as uLMS is less hormone sensitive than fibroids [47].

Should Adjuvant Pelvic Radiotherapy Be Used in uLMS?

The role of adjuvant pelvic radiotherapy (APRT) following surgery in uLMS is controversial. Available data have been limited to small retrospective series, frequently with mixed histologies, which has made it difficult to objectively evaluate the role of radiotherapy. However, more recently a number of population-based studies have been published, which have provided useful information on larger numbers of

patients. Kapp et al. reported on 1,396 patients with uLMS from the Surveillance, Epidemiology, End Results (SEER) database treated between 1988 and 2003 [11]. Almost all patients received primary surgery (96.4 %), and 310 (22.2 %) received APRT. Radiotherapy had no impact on 5-year disease-specific survival, but no data were available on local control rates. A further population-based study reported on 3,650 patients from the National Oncology Database, contributed to by 130 American hospitals. This study included 920 patients with uLMS and showed an improvement in locoregional failure-free survival with the addition of APRT from 84 to 98 % ($p<0.01$), although it had no impact on overall survival [48].

There has been a single prospective randomized phase III study of the role of APRT in uterine sarcomas, carried out by the European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group (EORTC CCG), comparing it to observation in FIGO stage I and II disease [49]. The study took 13 years to accrue 224 patients, which included 99 uLMS patients. Radiotherapy was associated with fewer local relapses for the whole group (24 versus 44 relapses for APRT or observation, respectively), although it had no effect on either progression-free survival (PFS) or overall survival (OS). When the uLMS group was reported separately, the effect on local control was lost, with local relapse rates of 20 % versus 24 % for radiotherapy and observation, respectively. Interestingly, isolated local recurrences were reduced from 14 % in the observation group to 2 % in the radiotherapy group, but distant metastases were more frequent in the radiotherapy group (36 % versus 14 % in the observation group). The authors concluded that there was no benefit for APRT in the uLMS group. It has subsequently been suggested that the higher rate of distant metastases in the APRT group may reflect that radiotherapy improves local control and so changes the patterns of relapse and also that the patients with smaller FIGO stage I tumors may be those expected to derive most benefit from APRT, as having a lower risk of distant metastases than those with larger tumors [50].

In summary, APRT may improve local control in uLMS patients, but there is no associated survival benefit, because radiotherapy will not affect the risk of distant relapse, which will be determined by prognostic factors such as age, grade, stage, and lymph node positivity. Thus, APRT is probably best avoided unless an individual is at particularly high risk of local relapse, for example, positive resection margins, or perioperative contamination by morcellation.

What Is the Current Status for Use of Adjuvant Chemotherapy in Uterine Leiomyosarcomas?

When patients with uLMS relapse, there is frequently a distant component, such that adjuvant chemotherapy is an attractive intervention to try to reduce such relapses. There has been one prospective randomized phase III study of adjuvant chemotherapy in uterine sarcomas [51]. This study randomized 156 patients following hysterectomy to 8 cycles of doxorubicin versus observation. No difference was seen between the treatment groups for rates of recurrence, progression-free, or overall survival. However, there were a number of shortcomings to this study. It included a range of histologies, with only 48 uLMS; the chemotherapy schedule would now be considered suboptimal for adjuvant chemotherapy in soft tissue sarcoma (STS), and the small size of the study suggests that it may well have been underpowered to detect a benefit from adjuvant chemotherapy. Thus, the negative result indicates that the hypothesis has not been adequately tested rather than disproved.

In the absence of further randomized studies, the STS literature can offer some insights, as many patients with uLMS were treated within STS adjuvant chemotherapy studies. In 1997 a meta-analysis was published of adjuvant chemotherapy studies, including 1,568 patients from 14 trials, with 263 patients with uLMS, using a range of different doxorubicin-based chemotherapy schedules [52]. Statistically significant hazard ratios were observed for local relapse-free interval, distant relapse-free interval, and overall recurrence-free survival. However, the absolute benefit for overall survival was only 4 %, with a nonsignificant hazard ratio of 0.89 ($p=0.12$), representing an absolute benefit of 4 %. The EORTC subsequently carried out a large study of adjuvant chemotherapy in STS, using 5 cycles of doxorubicin 75 mg/m^2 and ifosfamide 5 mg/m^2 with growth factor support, compared with observation [53]. However, again, no benefit from adjuvant treatment was seen, with 5-year relapse-free rates of 51 and 53 % ($p=0.487$) and overall survival rates of 64 and 69 % ($p=0.935$) for chemotherapy and observation arms, respectively.

In recent years, the combination of gemcitabine and docetaxel has been shown to be active in phase II studies in advanced/metastatic uLMS [54–56]. This led to a small phase II study of the schedule used as adjuvant treatment in resected uLMS patients [57]. Twenty-five patients received 4 cycles of chemotherapy, and 45 % were progression-free at 2 years. Of the 18 patients with stage I and II disease, 59 % were progression-free at 2 years. These promising results have led to development of a phase III study protocol in a unique international collaboration between the National Cancer Institute (NCI) in the USA, the EORTC, and Cancer Research UK as part of the International Rare Tumour Initiative (IRCI). The study compares 4 cycles of gemcitabine and docetaxel, followed by 4 cycles of doxorubicin, in resected FIGO (2009) stage I uLMS, with observation.

In summary, there is insufficient evidence for the routine use of adjuvant chemotherapy in uLMS, and ideally patients should be entered into clinical trial protocols such as the international collaborative study described above. Such collaboration is essential to recruit sufficient patient numbers in such a rare tumor subtype.

Recurrent/Metastatic Disease

Is There a Role for Surgery for Recurrent/Metastatic Disease in uLMS?

Most uLMS that recur do so within 2 years after primary treatment. Given the aggressive nature of the disease, and tendency towards systemic relapse, surgery is undertaken only infrequently. However, secondary cytoreductive surgery can be considered with the aim of prolonging survival for selected patients with a limited localized relapse, of good performance status, and with a disease-free interval of at least 6 months [58].

Pulmonary metastasectomy is successfully utilized in selected patients with STS [59], and this certainly includes uLMS. In a study including 103 recurrences of gynecologic tumors (40 were sarcomas), pulmonary metastasectomy has been shown to be safe and effective [60]. The median time interval between the first gynecologic procedure and pulmonary resection was 24 months (range, 0–237 months). The authors recommend that pulmonary metastasectomy should be considered in patients with no evidence of recurrent disease at the primary site and no other distant metastases, with a limited number of pulmonary metastases, and in patients with adequate pulmonary reserve.

What Is the Role for Palliative Chemotherapy in uLMS?

The standard of care for systemic chemotherapy in locally advanced or metastatic STS is doxorubicin, with or without ifosfamide, and has remained unchanged over three decades [61, 62]. Combining agents can sometimes increase objective response rates, but at the expense of greater toxicity. However, it is not known whether combination chemotherapy is associated with a survival benefit over single-agent chemotherapy. The EORTC have recently completed a study (EORTC 62012) that aimed to answer this question by comparing doxorubicin with doxorubicin and ifosfamide in advanced STS.

In recent years an important development in STS has been the recognition of differential responsiveness of distinct histological subtypes to particular systemic agents rather than treating all STS as a single group; leiomyosarcoma is a good example of this concept. In 2002, an important study was published of the combination of fixed-dose rate gemcitabine and docetaxel in 35 patients with unresectable leiomyosarcoma, of whom 29 had uLMS [54]. An impressive overall response rate of 53 % was observed, with a median time to progression of 5.6 months, and the authors concluded that the combination was highly active. This study generated significant interest in the combination and led to a number of further studies, both in leiomyosarcoma and in STS generally. The Gynecologic Oncology Group (GOG) in the USA subsequently carried out two phase II studies of this combination specifically in uLMS, in first-line [56] and second-line [55] settings, showing median PFS of 4.4 months and 5.6+ months, respectively, confirming activity in this patient group.

Trabectedin was licensed in 2007 by the European Medicines Agency for use in STS following failure of doxorubicin and ifosfamide chemotherapy. Pivotal to this was a randomized phase II study of trabectedin in 270 patients with advanced L-sarcomas (liposarcoma and leiomyosarcoma) with 32 cases of uLMS, evaluating two different treatment schedules [63]. The study showed that while both schedules were active, the 3-weekly 24-h schedule was superior, with a median PFS of 3.3 versus 2.2 months and a median OS of 13.9 versus 11.8 months. The RECIST (response evaluation criteria in solid tumors) response rate was a modest 5.6 %, but the importance of trabectedin appears to be the ability to achieve potentially prolonged stable disease. The authors concluded that trabectedin was "an important new option to control advanced sarcomas." These results have been confirmed with the publication of outcomes from a worldwide expanded access program of trabectedin in 1,895 patients with STS, showing longer overall survival for L-sarcomas compared with other STSs (16.2 versus 8.4 months) [64]. Two further studies have assessed trabectedin specifically in uLMS. A retrospective study of 66 patients with advanced pretreated uLMS confirmed the activity seen in the randomized phase II study [65]. The GOG carried out a formal phase II study of 20 patients with advanced recurrent uLMS. The objective response rate was 10 % (2/20), with a median PFS of 5.8 months and median OS of >26.1 months. The study had a standard two-stage design and required 3 responses to go on to the second stage. This was not met, and so the study was stopped on completion of the first stage. The authors concluded that the activity of trabectedin was "modest," although the "duration and rate of stable disease is interesting." In fact, the results were very consistent with the previously discussed studies, which had concluded trabectedin to be active. The variance of the conclusions demonstrates the pitfalls of relying on objective response rate rather than PFS as the primary end point for identifying active agents in STS.

What Is the Role for Targeted Therapies in uLMS?

A number of targeted agents have been evaluated in advanced/metastatic STS, including uLMS. Those furthest in development have been the mTOR inhibitor ridaforolimus and the vascular endothelial growth factor receptor inhibitor pazopanib. The large phase III SUCCEED trial has evaluated the role of ridaforolimus as a maintenance therapy following response to conventional chemotherapy in 711 patients with STS and bone sarcoma [66]. Median PFS was increased by 21 % (HR 0.72, $p=0.0001$), but the absolute benefit was only 3.1 weeks, raising the question as to the clinical relevance of this statistically significant result. Pazopanib has been evaluated in the PALETTE study, a prospective phase III placebo-controlled trial of 369 patients, which demonstrated a significant prolongation of PFS from 1.6 to 4.6 months, HR 0.31 ($p<0.0001$) [67]. Pazopanib has been licensed for use in relapsed STS in the USA and Europe in 2012 and is an important addition to treatments for STS and uLMS.

Is There a Role for Hormonal Therapy in uLMS?

As discussed previously, uLMS expresses estrogen and progesterone receptors in a relatively high proportion of patients (Table 28.2), which has led to interest in using hormonal therapies in patients with advanced/metastatic disease. There have been a small number of case reports of responses to progestagens [68–70] and aromatase inhibitors [71]. A retrospective study of 34 patients with metastatic uLMS treated with aromatase inhibitors for 1–84 months' duration showed a partial response in 9 % and stable disease in 32 % [33]. The median PFS was 2.9 months, with a 1-year progression-free rate of 26 % for receptor-positive tumors. Patients with low-grade tumors derived greater benefit, with a 1-year progression-free rate of 60 % compared with 13 % for high-grade tumors. A prospective phase II study of letrozole in hormone receptor positive uLMS recruited 26 patients before it was closed early due to failure to accrue [72]. Results were similar, with a median duration of study treatment of 2.2 months, with a median PFS of 2.8 months, with greatest benefit for patients with greater receptor positivity. Neither of these studies has definitively shown activity of aromatase inhibitors in uLMS, although there may be benefit in strongly receptor-positive tumors. The failure to complete the phase II study again emphasizes the importance of international collaboration to complete such studies, and a further phase II study is being planned by the International Rare Cancer Initiative discussed previously.

Endometrial Stromal Sarcoma

Epidemiology and Diagnosis

Historically, ESS was also designated lymphatic stromal myosis or endometrial stromatosis [73, 74]. It accounts for approximately 20 % of all uterine sarcomas, with an incidence a third of that of uLMS [4]. It usually occurs in middle-aged women, at a median age of around 50 years [4, 75], and typically presents with abnormal uterine bleeding and pelvic pain [10]. The majority (60 %) of cases present with FIGO stage I disease, with only 20 % presenting with stage IV metastatic disease [75]. The natural history is one of slow-growing indolent disease, and this is reflected by good outcomes, with a large population-based study of 831 patients reporting a 5-year disease-specific survival of >90 % for all stages [75] and a smaller patient series of 85 patients reporting 5- and 10-year crude survival rates of 84 and 77 % for stage I disease [76]. However, late relapses are relatively common, necessitating long follow-up for these patients.

Similar to uLMS, imaging modalities are unreliable in making a preoperative diagnosis of ESS, and there is a need for more effective imaging techniques in order to improve the accurate preoperative diagnosis of ESS.

Histopathology

Endometrial stromal neoplasms can be either benign (endometrial stromal nodule, ESN) or malignant (ESS). ESS behaves as a "low"-grade sarcoma, with the potential for recurrence and metastasis [77]. Endometrial stromal neoplasms are exclusively composed of cells resembling the endometrial stroma in its proliferative phase. The rare ESN has well-circumscribed borders [78, 79], whereas ESS represents the same histological entity, but with infiltrating borders [77]. Typical microscopic findings include a uniform population of endometrial stromal-type cells invading the myometrium and myometrial vessels. Until recently, ESS was subdivided into low-grade and high-grade tumors, on the basis of mitotic count [78]. However, high-grade tumors lack the typical growth pattern and vascularity of ESS and show destructive myometrial invasion rather than the lymphatic permeation of ESS. Moreover, they demonstrate marked cellular pleomorphism and brisk mitotic activity. As a result, the term ESS is now restricted to malignancies that were formally referred to as low-grade ESS [77, 79].

ESS is characterized by a chromosomal translocation t(7:17)(p15;q21) which results in the juxtaposition of two zinc finger genes JAZF1 and JJAZ1 resulting in the JAZF1/JJAZ1 fusion gene. One study found the translocation in 7/7 cases of ESS, 3/3 cases of ESN, but only 3/7 cases of UES [80]. Subsequent studies have confirmed these findings, with translocations detected in 8/16 cases of ESS and 4/4 ESN [81] and 6/12 cases of ESS but only 1/9 cases of UES [39]. The presence of the translocation in ESN suggests that ESS may arise from a progression of a benign stromal proliferation. However, the lack of the translocation in the majority of cases of UES suggests that this disease may not always be due to malignant progression of ESS, but occurs via a distinct pathogenetic mechanism in at least some cases. While only approximately half of ESS cases have the JAZF1/JJAZ1 translocation, two other fusion genes have now been identified as associated with ESS, JAZF1/PHF1 and EPC1/PHF1 [82].

Early-Stage Disease

What Is the Role for Oophorectomy, Lymphadenectomy, and Cytoreductive Surgery in ESS?

Surgery with hysterectomy is the cornerstone of treatment for localized ESS. As imaging studies cannot reliably diagnose ESS preoperatively, surgical resection for a presumed fibroid is a common scenario. This can result in inadvertent tumor morcellation of ESS, a technique used for presumed benign disease, which has an adverse impact on the patient outcomes [83, 84]. Although in the case–control series of Park et al., morcellation resulted in a higher rate of

abdominopelvic recurrences, patients could be salvaged by surgical resection such that 5-year overall survival was equivalent for patients undergoing hysterectomy or morcellation (83 % versus 92 %, $p=0.9$) [84]. These data support that ideally patients should undergo complete resection with hysterectomy to ensure an optimal outcome.

The benefit of lymphadenectomy for ESS is controversial. Nodal involvement designates a higher stage of disease and results in a worse outcome [75]. The incidence of lymph node metastases in ESS is generally low, with rates of 9.9 % (28/282) [75] and 7 % (7/100) [85] in recent series. Systematic lymphadenectomy in ESS does not appear to confer a therapeutic benefit [75, 85–87] and therefore is not indicated unless lymph nodes are pathologically enlarged.

Another controversial issue is the need for oophorectomy. Traditionally, the ovaries were removed because ESS typically expresses estrogen and progesterone receptors and there were concerns of higher relapse rates if the ovaries were retained. In contrast to previous belief, it appears from small [36, 86, 88–91] and large [75, 85] series that leaving the ovaries in situ does not worsen survival. This is important for premenopausal women who can safely avoid oophorectomy, which may improve their quality of life.

The benefit of cytoreductive surgery in locally advanced ESS is controversial, with little published evidence to support the practice. However, knowledge of tumor biology and natural history (indolent disease with primarily transperitoneal spread) suggests that cytoreductive surgery, including removal of ovaries, might be beneficial because of the "low-grade" nature of the disease and the efficacy of additional hormonal therapy [36, 92, 93]. Extensive surgery with organ resection (e.g., splenectomy, bowel resection) can be considered, particularly if this contributes to achieving complete resection with no residual tumor. However, the impact of resection of locally advanced disease on prolongation of survival is not proven, and so the decision to undertake extensive resections should be taken on an individual patient basis, depending on the relative morbidity of such surgery.

Should Adjuvant Pelvic Radiotherapy Be Used in ESS?

For many years there had been little information to inform decisions about the use of APRT in ESS, as published series have been small and uninformative. The single prospective randomized controlled study of APRT in uterine sarcomas included only 30 patients with ESS and so had insufficient power to draw conclusions [49]. However, a number of larger retrospective database studies have been recently published. Two studies have utilized the SEER database of the NCI in the USA [75, 87]. One study evaluated 831 women with ESS treated between 1988 and 2003, of grades 1–4 (it is assumed that grades 1 and 2 represent ESS, and grades 3–4 UES). Of these, 24.7 % received APRT. There is little further detail, but comment is made that radiotherapy had no demonstrable impact on overall survival [75]. A further study reported on 1,010 patients with ESS within the SEER database treated between 1983 and 2002, specifically evaluating the role of APRT [87]. It showed that radiotherapy had no impact on 5-year cause-specific survival (80.1 and 90.7 % for surgery and radiotherapy versus surgery alone, respectively) or overall survival (72.2 and 83.2 % for surgery and radiotherapy versus surgery alone, respectively). The lack of benefit was irrespective of FIGO stage, age, or tumor grade. The largest published study to date included 3,650 patients with uterine sarcoma within the National Oncology Database in the USA. Of 361 patients with ESS, 30 % had APRT, with a small improvement of locoregional failure-free survival at 5 years from 93 to 97 % ($p<0.05$). However, as with the previous two studies, it had no impact on overall survival [48].

In summary, despite the recent publication of three large population-based studies, there is no evidence that APRT improves overall survival in ESS and only modest evidence that it improves locoregional tumor control, which appears to be excellent in any case following surgery alone. Thus, at present there seems little justification to recommend routine use of APRT following complete excision of disease.

Should Adjuvant Hormonal Therapy Be Used in ESS?

There is a high rate of hormone receptor positivity in ESS (Table 28.2), which has led to interest in using hormonal therapies for both advanced disease and adjuvant therapy in early-stage disease. A small study reported on 22 patients with ESS, of whom 31 % (4/13) of patients receiving adjuvant progestins recurred, compared with 67 % (6/9) recurrence in patients who did not receive hormonal therapy [36]. Another study of 30 patients who received adjuvant hormones showed a nonsignificant trend to improved overall survival of 97 months for patients receiving hormonal therapy as compared with 72 months for those who did not ($p=0.07$) [92]. Amant et al. reported on 31 ESS patients, showing benefit for patients with stage III/IV disease, of whom only 1/5 patients receiving adjuvant hormonal therapy relapsed, as compared with 3/4 who did not, concluding that adjuvant hormonal therapy lowered recurrence rates and improved overall survival [86]. Only 2 of 22 patients with stage I disease received adjuvant hormones, so it was difficult to draw conclusions for this group. Nevertheless, the authors concluded that the high rates of recurrence of ESS support the current practice in some centers to give adjuvant hormonal treatment. This seems reasonable, given that hormonal therapies are generally well tolerated and that it is unlikely that a clinical of trial of adjuvant therapy could be carried out given the rarity of ESS. However, several questions remain, such as optimal regimen and duration of therapy.

Metastatic/Recurrent Disease

Surgery

Recurrences of ESS are common even in early-stage disease, particularly in the lungs and abdomen. Relapse can occur in 36–56 % of patients with early-stage disease, with a median time to recurrence of 65 and 9 months for stages I and III–IV, respectively [36, 74, 77]. Although valid data are lacking, repeat surgery for a disease that is indolent and hormone sensitive appears to be an acceptable approach. Secondary and tertiary cytoreductive procedures, including resection of distant metastases, should be considered [94–96]. Intervals between surgeries can be extended by the addition of hormonal therapies [10, 97].

Palliative Hormonal Therapy

As discussed previously, there are high rates of expression of estrogen and progesterone receptors in ESS, leading to hormonal therapies being used for advanced or metastatic disease. There are a number of case reports and series showing responses to progestins [29, 36, 98, 99], gonadotrophin-releasing hormone agonists [100], and aromatase inhibitors [29, 101, 102]. The largest series describes 30 patients with recurrent ESS treated with hormonal therapy until disease progression [10]. Five (17 %) patients achieved a complete response, 3 (10 %) a partial response, and 16 (53 %) stable disease. The median time to progression was 24 months. Thus, hormonal therapies appear to be effective for metastatic disease, at least for a period of time, with high proportions of patients deriving benefit. Ideally a prospective clinical trial needs to be carried out, and the currently ongoing PARAGON study is aiming to address the question of efficacy of aromatase inhibitors in potentially hormone responsive recurrent or metastatic gynecological neoplasms, including endometrial stromal sarcoma (http://www.anzgog.org.au/trialdetails.aspx?trialno=16).

Is There a Role for Palliative Chemotherapy in ESS?

There is little evidence reported on the use of chemotherapy in metastatic ESS, and the literature is difficult to interpret because for early studies it is difficult to know whether patients had ESS or UES, because of the changes in histopathological terminology. In a GOG study of doxorubicin +/− dacarbazine in advanced gynecological sarcomas, an 18–20 % response rate was observed in the "other" sarcoma group (of which 73 % were "ESS") [103]. Piver et al. reported on patients with recurrent endolymphatic stromal myosis (which would now be termed ESS), including two patients who had durable responses to doxorubicin, methotrexate and megestrol acetate, and doxorubicin and chlorambucil, respectively. However, another ten patients failed to respond to chemotherapy [74]. More recently, Cheng et al. reported on ten patients with recurrent ESS who received a range of chemotherapy regimens including doxorubicin, gemcitabine and docetaxel, actinomycin D, and paclitaxel and liposomal doxorubicin. Four patients achieved stable disease, but 6 showed disease progression, with a median time to progression of 6.5 months [10]. Thus, chemotherapy does seem have some activity in ESS, but fewer patients appear to benefit than those treated with hormonal therapies. It may be that chemotherapy is more suitable for patients with more aggressive and rapidly progressing disease, although this is speculative.

Palliative Radiotherapy

Palliative radiotherapy can be used for recurrent or metastatic ESS, if the disease is encompassable within radiotherapy portals and can be effective in this setting [10]. However, it is likely that most recurrences will be treated surgically if localized, or with systemic therapy if disseminated, such that the role for radiotherapy is limited.

Undifferentiated Endometrial Sarcoma

Epidemiology and Diagnosis

UES is the rarest of the uterine sarcomas, accounting for only 6 % of a recent series of uterine sarcomas [4]. These are aggressive tumors that present at higher stages and in older patients than ESS, with 48 % presenting as FIGO stage I/II, and 33 % as stage IV, at a median age of 60 years [85]. Outcomes are much poorer than for ESS, with reported 5-year disease-specific survival rates of 29–43 % [75, 76, 89] and 5-year overall survival of 25 % [85]. In a recent study [4], the presence of vascular invasion was the only statistically significant prognostic factor.

As with uLMS and ESS, preoperative diagnosis is challenging, and frequently the diagnosis is made following surgery. From a practical point of view, these high-grade tumors show similarity with uLMS with respect to clinical presentation and treatment modalities.

Histopathology

The designation poorly differentiated or undifferentiated endometrial sarcoma (UES) refers to endometrial sarcomas without recognizable evidence of a definite endometrial stromal phenotype [73, 79, 104]. Very little is known of these malignancies because studies are characterized by small numbers, there is a lack of standardization of pathologic criteria, and outcomes are frequently mixed with those obtained in ESS. UES do not show evidence of gene-specific fusions, suggesting that these tumors arise by a different pathogenetic mechanism from ESS [105]. Immunohistochemical data are also sparse, including only a few cases per article published. UES have been shown to

express PDGFRA [106], androgen receptors [107], WT1 [108, 109], and ERBB-2 (HER-2/NEU) [110]. A broad panel of immunohistochemical markers was recently tested in uterine sarcomas, but most were negative in UES [111].

Early-Stage Disease

What Is Optimal Surgery in UES?

UES is an aggressive tumor with a tendency towards distant hematogenous metastases to liver and lungs, so full preoperative staging is required. Standard treatment for early-stage UES is hysterectomy [112]; although the ovaries are only involved in advanced-stage disease, they are usually removed in this predominantly postmenopausal group of patients. Lymph nodes are only involved in advanced-stage disease, and so removal in early-stage disease is not necessary.

Is There a Role for Adjuvant Pelvic Radiotherapy in UES?

It is difficult to comment specifically on the role of APRT in UES, because there are few series that report specifically on UES rather than on endometrial sarcomas generally. Furthermore, it is recognized that most recurrences after initial treatment for early-stage ESS occur at distant sites [89], calling into question the benefit of APRT. Weitmann et al. reported on 17 patients with "grade 3 ESS," of whom 12 received APRT. Only 3/12 patients recurred, all distantly but only 1 also locally, and so the authors advocated the use of APRT. Schick et al. reported on 29 patients with UES of whom 25 (86 %) had APRT to a median dose of 45 Gy and comment that APRT had a significant beneficial effect on progression-free and overall survival on multivariate analysis, although specific details are not given [76]. Leath et al. reported on 31 UES patients of whom 12 received APRT, but of these 50 % subsequently recurred [92]. Thus, it is not possible to make specific recommendations on the role of APRT, although the threshold for its use is inevitably low, given the high rates of tumor recurrence, and certainly the current USA National Comprehensive Cancer Network (NCCN) guidelines for uterine sarcomas (version 3.2012) state that radiotherapy can be "considered" [113].

Should Adjuvant Chemotherapy Be Used in UES?

The concept of adjuvant chemotherapy in UES is attractive because of the high risk of distant relapse and poor survival. However, as with APRT, there is little reliable published information to guide practice. However, recent series suggest that adjuvant chemotherapy is being used in some patients [76, 89, 114, 115]. For example, Schick et al. reported that 12/26 (46 %) of patients received adjuvant ifosfamide-based chemotherapy, with a 43 % disease-specific survival [76]. The NCCN guidelines for uterine sarcomas (version3.2012) again state that adjuvant chemotherapy can be "considered" [113].

Recurrent/Metastatic Disease

Should Surgery Be Considered for Recurrent/Metastatic Disease?

The treatment of recurrent or metastatic disease is decided on an individual patient basis. Disease is usually extensive and widely invasive such that surgery is only possible in a small minority of patients with UES. In addition, unless complete excision of disease can be achieved, there are significant concerns that disease will simply rapidly regrow following surgery. Patients should be selected carefully, with surgery best reserved for cases where there is minimal or single-site disease, with a disease-free interval of more than 6 months, in patients of good performance status [45, 58].

Palliative Chemotherapy and Radiotherapy in UES

Outcomes for patients for locally advanced/metastatic disease in UES are very poor [76, 89]. Chemotherapy can be used for palliation of symptoms and disease control, and in general the same regimens are used as for metastatic uLMS [113] (see earlier section). Hormonally therapies are generally not used, as UES frequently does not express hormone receptors, and the disease is aggressive and too rapidly growing to await a response. Palliative radiotherapy can be used but is likely to be suitable in only a few patients because of the diffuse nature of disseminated disease.

Conclusions

Uterine sarcomas are uncommon and there have been few prospective randomized studies. For all uterine sarcomas, preoperative imaging is unable to reliably establish the diagnosis in early-stage disease. Given the heterogeneity of diseases and differences in tumor biology, individualization of management is essential. Whereas ESS is typically a low-grade disease with an indolent behavior, uLMS and UES behave as aggressive high-grade malignancies with a propensity for early dissemination. For advanced/metastatic or recurrent uLMS and UES, judging the balance between palliative chemotherapy and quality of life is essential. Many uncertainties remain as to the optimal management of these different diseases, and international collaborative studies are needed to provide new insights. The International Rare Cancer Initiative aims to use the networks of existing trial groups and has a program for uncommon uterine mesenchymal malignancies and is essential if progress is to be made in these rare tumors. Such an initiative has the potential to collect clinical data and tumor specimens within prospective studies that together will allow the in-depth study of uterine sarcoma tumor biology.

Concluding Comments

- International collaboration within the International Rare Cancer Initiative has already resulted in clinical trials into uterine sarcomas.
- Such international collaborative efforts are essential to make progress in understanding the biology and optimal management of such rare tumors.
- Optimal management needs to reflect the very distinct biological behaviors of the different histological subtypes of gynecological sarcomas.
- In particular, it is important to recognize that systemic therapies must take into account different histological subtypes, and future clinical trials should incorporate this in their design.

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What Is the Future of Immunotherapy in Ovarian Cancer?

29

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Summary Points

- Active versus passive immunization.
- Public versus private antigen targeting.
- Naturally occurring TILs versus engineered T cells.
- Single therapy versus combinational approach.

Background and Introduction

Although not traditionally considered immunogenic, increasing evidence indicates that ovarian cancers are, in fact, immunogenic tumors and are responsive to immunotherapies. Three distinct categories of data support this claim. First, there is accumulating evidence of spontaneous antitumor immune responses and of their association with longer survival in a proportion of ovarian cancer patients. Second, and conversely, there is evidence of active tumor immune evasion mechanisms and their association with short survival in some ovarian cancer patients. And finally, preclinical as well as clinical data have now demonstrated that immunotherapy can be efficacious against these cancers.

It is now clear that spontaneous antitumor immune responses exist in many ovarian cancer patients. Tumor-reactive T cells and antibodies have been detected in peripheral blood of patients with advanced stage disease at diagnosis [1, 2], while oligoclonal tumor-reactive T cells have been isolated from tumors or ascites [3–11]. The tumor rejection antigens expressed by ovarian cancer have not been thoroughly characterized. Among the most promising candidates are cdr2, mesothelin, and NY-ESO-1 [12–14]. Several additional well-known tumor-associated antigens are recognized by peripheral blood or tumor-associated lymphocytes of many ovarian cancer patients. These include p53; HER2/neu; folate receptor-α; cancer-testis antigens such as the MAGE melanoma antigen family members and sperm surface protein Sp17; mucins or glycoproteins such as Lewis(y), sialylated-Tn, CA-125, and MUC-1; and universal tumor antigens such as survivin and hTERT [15]. Importantly, the detection of an antitumor immune response in the form of intraepithelial (also called intratumoral) tumor-infiltrating lymphocytes (TILs), i.e., T cells infiltrating tumor islets, predicts significantly longer survival in ovarian cancer. We first reported in an Italian cohort that patients whose tumors had intraepithelial T cells experienced longer progression-free and overall survival as compared to patients whose tumors lacked intraepithelial T cells [16]. Survival at 5 years was substantial (38 %) in patients whose tumors had intraepithelial T cells ($n=102$) and negligible (4.5 %) in patients lacking them ($n=72$), even after complete response to chemotherapy. A signature of antitumor immune response activation was identified in tumors with intraepithelial T cells [16]. The impact

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of intraepithelial $CD3^+$ or $CD8^+$ T cells was confirmed by multiple independent studies on ethnically and geographically diverse populations [17–21]. Importantly, intraepithelial T cells were more prevalent in tumors with increased proliferation, indicating that improved outcome is not due to indolent tumor cell behavior [17].

Significant progress has been made recently in our understanding of immune evasion mechanisms operating in some patients with ovarian cancer. $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory (Treg) cells were first demonstrated in ovarian cancer [22, 23], where increased Treg frequency predicts poor patient survival [20, 23]. Immunosuppressive B7-H4 expressing macrophages were recently found to correlate with survival in ovarian cancer [24]. In addition, ovarian cancer cells express programmed death ligand 1 (PD-L1 or B7-H1), a ligand for the immunosuppressive T-cell receptor PD1, which blocks T-cell responses. Expression of PD-L1 by tumor cells predicted paucity of intraepithelial TILs and short overall survival in ovarian cancer [19]. Further, overexpression of the endothelin B receptor (ET_BR), which suppresses T-cell-endothelial adhesive interactions and T cell homing to tumor, correlated with absence of TIL and short survival in ovarian cancer [25, 26]. Finally, a recent study segregated high- and low-risk ovarian cancer patients based upon their tumor gene signature and found a strong correlation between decreased expression of immune genes and the development of high-risk tumors. In particular, high-risk tumors often displayed downregulation of genes involved in antigen processing and presentation [27].

The association of antitumor immune responses with prolonged survival and, vice versa, the association of immune escape mechanisms with poor survival suggest that ovarian cancers are intrinsically immunogenic. Indeed, ovarian cancers should no longer be considered immunologically inert tumors. Accordingly, pilot clinical data indicate that ovarian cancer patients can, in fact, respond to the same immunotherapy approaches as patients with other immunogenic tumors [28], including interleukin-2 (IL-2) [29, 30], anti-CTLA-4 antibody [31, 32], and adoptive transfer of ex vivo expanded TIL [33, 34]. Notably, each of these therapies is designed to exploit a preexisting endogenous antitumor immune response. Although, insufficient to reject tumor naturally, these responses can potentially be harnessed therapeutically. Here we will review three categories of immunotherapies which can be used to manipulate natural antitumor immunity or to induce new antitumor immune responses. These include cancer vaccines (active immunization), adoptive T-cell therapy (passive immunization), and nonspecific immunomodulation. Each targets immune cells in different ways. They can be used alone, together, or with conventional approaches for combinatorial tumor therapy.

Cancer Vaccines

As with many other tumor types, vaccines have been the primary approach to ovarian cancer immunotherapy so far [15, 35–37]. Consistent with experience in other immunogenic tumors [38], vaccines have shown limited efficacy as monotherapy in patients with advanced recurrent disease. Clearly, much work is required to improve their performance. Current efforts to improve vaccines are directed broadly towards (a) optimizing the choice of antigens, (b) improving vaccine delivery systems to maximize the magnitude and quality (phenotype and polarization) of T-cell response, and (c) developing combinatorial approaches with adoptive T cell or immunomodulation therapy to maximize activation and function of vaccine-primed T cells in vivo.

Pros

The results of some studies provide encouragement for further vaccine development. In a retrospective review of patients treated in the adjuvant setting after secondary complete response, Sabbatini and colleagues noted that patients vaccinated with monovalent or heptavalent vaccines against carbohydrate epitopes experienced significantly longer time to progression and higher progression-free survival rates relative to controls from the same institutions treated with alternative consolidation therapies [39]. In addition, vaccination with anti-idiotype ACA-125, an analogue of CA-125, resulted in CA-125-specific antibodies and was associated with prolonged survival [40]. Another study was performed using CEA-MUC-1-TRICOM poxviral-based vaccines in 16 patients including 3 ovarian cancer patients. Immune responses to MUC-1 and/or CEA were seen following vaccination in 9 patients. A patient with clear cell ovarian cancer and symptomatic ascites had a radiographically and biochemically durable (18-month) clinical response [41]. In another study, vaccination against HER2 has resulted in sustained antigen-specific T-cell and humoral immunity as well as epitope spreading in ovarian cancer patients [42].

An alternative to vaccines directed towards specific antigens is whole tumor antigen vaccines created using tumor cells, autologous tumor lysate, or tumor-derived RNA [43–45]. Tumor antigen preparations can be injected into patients directly, or they can be first loaded onto autologous dendritic cells. Advantages of these vaccines include the opportunity to induce immunity to a personalized and broad range of antigens, which could minimize the development of tumor escape variants, the inclusion of yet unidentified tumor rejection antigens, no HLA haplotype restriction, and the simultaneous administration of MHC class I and class II epitopes, which could prove beneficial for immunologic memory. In a pilot study using mature DCs pulsed with whole

autologous tumor lysate, three of six subjects demonstrated remission inversion, i.e., their progression-free survival post-vaccination was longer than the interval between pre-vaccine recurrence and prior chemotherapy treatment [46]. The use of DC/tumor cell fusion approach is a viable alternative whereby autologous DCs are fused with tumor cells, which allows DCs to express the entire antigen repertoire of the tumor cells to $CD4^+$ and $CD8^+$ T cells. DC/ovarian tumor cell fusions have been generated and demonstrated to be able to induce antitumor CTL activity in vitro [47].

Several groups have used viruses to increase tumor cell immunogenicity for whole tumor cell vaccination. Objective responses have been seen after intracavity delivery of a viral oncolysate vaccine generated with ovarian cancer cell lines infected with influenza A virus [48, 49] or with autologous tumor cells infected with Newcastle disease virus [50]. We also performed preclinical studies using replication-restricted herpes simplex virus (HSV) 1 to infect autologous tumor cells for vaccine preparation. HSV-infected tumor cells used directly or pulsed on dendritic cells elicited potent antitumor immune response in the mouse, which was superior to the use of UV-irradiated tumor cells [51–53]. Thus, whole tumor antigen vaccines can produce objective response if immunogenicity is increased through the use of pathogens.

Cons

A major limitation of cancer vaccines presently stems from the inability to elicit a rapid and overwhelming T-cell response, which is required to reject established tumors. This problem is magnified in ovarian cancer by the paucity of well-characterized rejection antigens to target and by the significant molecular heterogeneity of the disease [54]. Even when a defined target is available, and vaccination successfully induces an immune response, the long-term benefit can be limited by tumor evolution. In a recent study, one patient experienced complete objective response to NY-ESO-1 peptide vaccine, but later recurred with an NY-ESO-1-negative tumor, proving that single-target immunization can result in immune escape tumor variants following initial response [55].

A recent meta-analysis of 173 published, peer-reviewed immunotherapy trials revealed the low success rate of cancer vaccines to date. The trials involved patients with a variety of tumor types, including melanoma, renal cell and hepatocellular carcinomas, lung, prostate, breast, colorectal, cervical, pancreatic, and ovarian cancers. Patients received either molecular-defined antigens (synthetic peptides or proteins and viral or plasmid vectors encoding peptides or proteins; 1,711 patients) or whole tumor antigen (autologous or allogeneic tumor cells, dendritic cells pulsed with tumor extracts or mRNA; 1,733 patients). Overall, the authors calculated that 8.1 % of patients vaccinated with whole tumor antigen had objective clinical responses while 3.6 % of patients vaccinated with molecularly defined tumor antigens had objective clinical responses ($p < 0.0001$, chi-square test) [56].

Although whole tumor vaccines offer distinct advantages, some drawbacks warrant consideration. First, surgical procurement of large numbers of autologous tumor cells may not be possible in many patients. Alternatives to this limitation exist, including use of allogeneic cell lines or the use of tumor mRNA. RNA electroporation of DCs is a convenient approach to generate a potent tumor vaccine [52]. An additional concern with whole tumor vaccination relates to the inclusion of a large number of "self" antigens, which could potentially drive tolerogenic responses, i.e., expand Treg rather than cytotoxic lymphocyte responses. Recent work has demonstrated that DCs can be polarized ex vivo with the use of interferons, Toll-like receptor agonists, or p38 mitogen-activated protein kinase (MAPK) inhibitors to drive cytotoxic lymphocytes and Th17 effector cells at the expense of Treg [57]. On the other hand, if immunization is successful, there may be increased concern for breaking tolerance to "self" antigens, leading to immunopathology. To date, pilot studies with whole tumor vaccines have reported no autoimmunity in patients with ovarian cancer.

There is a controversy in the choice of target antigen with cancer vaccines and adoptively transferred T cells, as well. In the past few decades, shared (also known as "public") tumor-associated antigens have been the favored target of various immunotherapy strategies. This approach has been based largely on studies with melanoma [58]. This leads to the concept of "dispensable tissues," meaning that in order to achieve tumor eradication, it was necessary to expect tissue-specific toxicity damaging normal tissues [59]. As the expression of these antigens was shared between most individuals, this would make the manufacturing of a universal vaccine a possibility. However, recent advances in the clinical application of immunotherapy suggest that immunotherapy with "personalized" antigens (that arise from mutations) with preexisting immunity, which are designed to stimulate antigen-specific memory T cells, could also be expected to induce rapid and strong secondary immune responses (reviewed in [60, 61]). The current view is that both approaches, targeting public or targeting private antigens, can be beneficial either in cancer vaccines or adoptive T-cell therapy, but to increase the clinical benefits, special attention should be paid to the immunological status of each patient by characterizing the preexisting immune responses to the targeted antigens before immunotherapy.

Adoptive T-Cell Therapy

Effective cancer immunotherapy is dependent on the presence of large numbers of antitumor lymphocytes with appropriate homing and effector functions that enable them to seek out and destroy cancer cells in vivo. The adoptive transfer of

ex vivo expanded tumor-reactive T cells holds the potential of achieving this condition in a short period of time. Clinical trials testing spontaneous or induced polyclonal or oligoclonal T cells conducted in the past two decades have provided crucial lessons that can guide further optimization. The use of ex vivo expanded TILs has yielded promising clinical results. Based on animal studies showing that host lymphodepletion prior to T-cell transfer enhances persistence of T cells and antitumor responses, a scheme of incremental lymphodepletion through high dose non-myeloablating chemotherapy and added whole-body radiation was tested. Infused cells were both long lived and highly penetrating, showing regression of voluminous metastatic tumors, with up to 16 % complete response and 72 % overall objective response rates in recent reports with maximal lymphodepletion and radiation. T-cell persistence correlated with long lasting responses [38, 62]. Although these are phase I studies involving a highly selected cohort of patients with metastatic melanoma with preexisting antitumor immunity, whose tumors yield tumor-reactive TILs, the results clearly demonstrate the power of adoptive immunotherapy and dispel the assumption that immunotherapy can only control small tumors [28]. Furthermore, although the role of $CD8^+$ T cells has been well established in adoptive immunotherapy [38, 62], $CD4^+$ cells can also produce objective responses [63].

Currently, attempts to improve the efficacy of adoptive TIL therapy are focused on two areas: (a) optimizing methods to select tumor-reactive TIL and expand them under optimal costimulation conditions and (b) optimizing host and/or tumor conditioning. Findings from melanoma trials argue that use of memory rather than effector cells may be more efficacious for adoptive transfer [64]. In these key studies, although infused cells dominantly displayed a highly differentiated effector cell phenotype ($CD27^-$ $CD28^-$ $CD45RA^-$ $CD62L^-$ $CCR7^-$), TILs persisting 2 months after infusion in patients who exhibited tumor regression were characterized by a less differentiated phenotype ($CD27^+$ $CD28^+$ $CD45RA^+$ but $CD62L^-$ $CCR7^-$) and longer telomeres [65–69]. Mouse models confirm these findings [70]. Because TILs comprise a large number of tumor-reactive effector cells, identification of culture conditions that preferentially expand memory phenotypes is a priority. Recent technological advances with the development of artificial antigen-presenting cells (aAPCs) expressing a variable repertoire of costimulatory molecules and cytokines have generated new opportunities to provide the desired costimulatory molecules and cytokines to reeducate TILs, improving their potency and function in vivo. Carl June and colleagues have described the development of a next-generation K562-based aAPC platform capable of expressing multiple gene inserts, including human lymphocyte antigen (HLA)-A2; CD64 (the high-affinity Fc receptor), CD80, CD83, CD86, CD137L (4-1BBL), and CD252 (Ox40L); and a variety of T-cell supporting cytokines [71]. Cell-based aAPCs have proven to be more efficient at activating and expanding $CD8^+$ $CD28^-$ T cells, and antigen-specific T cells, than the magnetic bead-based aAPC [71].

TIL therapy is only possible for a fraction of patients. To generate TIL, a tumor mass must first be resected, which is not always possible. Additionally, that tumor mass must contain TIL, and those TIL must be responsive to the existing ex vivo expansion protocols. For many patients, these limitations make TIL therapy impossible. One strategy to make adoptive therapy available to a larger patient population involves engineering polyclonal T cells to redirect their specificity towards tumor antigens. This can be accomplished by transducing lymphocytes with a cloned T-cell receptor (TCR) of high affinity to tumor-associated epitopes. In this case, the cloned heterodimeric TCR is transduced to mixed peripheral blood T cells isolated from the patient, creating a large population of bispecific T cells, which are polyclonal with respect to their original TCR, but potentially monoclonal for the cloned TCR [72].

A second strategy to generate novel tumor-targeted T cells is to transduce the polyclonal population with receptors that recognize antigens in an MHC-unrestricted fashion. These so-called chimeric antigen receptors (CARs) are fusion genes encoding an extracellular domain that specifically binds to tumor epitopes through a single-chain variable fragment (scFv) linked to intracellular signaling modules (such as the CD3 zeta chain, TCRz) that mediate T-cell activation [72–74]. The scFv contains the V_H and V_L chains of an antitumor antibody joined by a peptide linker of about 15 residues in length, and it confers the parental antibody's specificity to the transduced T cells. In principle, universal targeting vectors can be constructed, because the scFvs bind to native cell surface epitopes and bypass the requirement for MHC restriction [75, 76]. Thus, in comparison to TCRs, CARs have two major advantages: (a) their HLA-independent recognition of antigen, which makes them broadly applicable regardless of the subject's HLA and regardless of the level of HLA expression on tumor cells, and (b) their signaling, which redirects T-cell cytotoxicity and permits T-cell proliferation and survival upon repeat antigen exposure. A potential drawback stems from their potential immunogenicity, if scFv are nonhuman. This can be averted by using human scFv.

Pros

There is evidence that TIL-based adoptive therapy is an important opportunity in ovarian cancer. In the early 1990s, ovarian cancers were found to yield reactive TILs after IL-2 culturing in vitro [77, 78]. Moreover, in pilot clinical trials, patients who received adjuvant therapy with adoptive transfer of tumor-derived lymphocytes expanded ex vivo with IL-2, following surgical debulking and frontline chemotherapy,

showed a survival advantage [33, 34]. Stage III EOC patients treated with consolidation adoptive transfer of expanded TILs after completion of cisplatin-based frontline chemotherapy ($n=13$) had a 3-year overall survival rate of 100 %, while that of a control group of patients ($n=10$) receiving only chemotherapy was 67.5 % ($p<0.01$). The 3-year disease-free survival rate of the patients in the TIL group and in the control group was 82.1 and 54.5 %, respectively. While these results can be limited by the lack of randomization, they nevertheless support the feasibility of adoptive therapy for ovarian cancer [33].

TCR-based engineering represents a potentially powerful strategy for ovarian cancer therapy as TCRs that recognize HLA-A2-restricted epitopes from known ovarian cancer antigens such as NY-ESO-1 and p53 are available for clinical testing as well [79–82]. Optimization through selection of naturally occurring or recombinant high-affinity receptors, engineering to prevent recombination with endogenous TCR, and the use of lentiviral vectors developed in the June lab with transfection efficiency above 90 % are poised to improve this approach significantly [83].

Adoptive transfer of T cells engineered to express chimeric receptors is also expected to be useful for ovarian cancer patients once the tools are refined. Some of the CARs investigated in vitro and in vivo target ovarian cancer antigens including FBP [84, 85], MUC-1 [86], HER-2, and mesothelin [87].

Cons

So far, there has only been a single study of adoptive transfer of CAR T cells in ovarian cancer [88]. Patients received autologous T cells which had been transduced with an FRα-specific CAR. While this study demonstrated safety, the results were disappointing. There were no clinically evident tumor responses—most likely due to low expression of the transgenic CAR and poor persistence of the transferred T cells [88]. However, strategies to address these issues are being developed. For instance, T-cell persistence can be dramatically improved by using human scFv and by adding costimulatory signaling capabilities to the intracytoplasmic domain of CARs. Indeed, one issue needing to be addressed with CARs is that signaling through the cytosolic domain of the usual scFv-TCRz construct does not fully replicate the multichain TCR signaling complex. This can be solved by incorporating additional signaling modules in the cytoplasmic domain of the chimeric receptor. The value of such innovations was recently demonstrated in a mouse xenograft model. Similar to the unsuccessful clinical trial, T cells were transduced with a CAR targeting FRα. However, in this study, the signaling domain of costimulatory molecule CD137 was added to the CAR's intracellular tail. When transferred into mice, these CAR T cells demonstrated enhanced in vivo persistence and tumor infiltration and achieved tumor regression superior to that seen in mice treated with T cells lacking the CD137 signaling domain [89].

Nonspecific Immunomodulation

Given the limitations of immunotherapy, there is a reason to hope that modulating immune checkpoints (Fig. 29.1) by activation of effector cells, depletion of Tregs, or activation of professional APCs could substantially improve the therapeutic efficacy of vaccines or adoptively transferred T cells. Certain chemotherapy regimens promote antitumor immunity through each of these mechanisms. Additionally, a number of nonspecific immunotherapies, including immunomodulatory cytokines, Toll-like receptor (TLR) agonists, and functional antibodies, are being developed to achieve these goals. Many of these nonspecific therapies may prove to be valuable adjuvants to more targeted immunotherapies, including vaccination and adoptive T-cell therapy.

Pros

The immunomodulatory effects of chemotherapy can be broadly grouped into three mechanisms. First, chemotherapy-induced tumor cell death can result in in situ vaccination. Drugs such as doxorubicin, idarubicin, mitoxantrone, and oxaliplatin induce immunogenic tumor cell death, which facilitates tumor antigen uptake by professional antigen-presenting cells and subsequent antigen presentation to antitumor T cells. Second, some chemotherapy drugs can also induce direct activation of antigen-presenting cells. Since the 1980s, it has been recognized that cyclophosphamide administered at standard dose prior to cancer vaccines significantly enhanced immunotherapy. However, the mechanism of this phenomenon was initially unclear [90]. A recent study in the mouse reported that a myelosuppressive dose of cyclophosphamide induces rebound myelopoiesis and leads to the emergence of tumor-infiltrating DCs that secrete more IL-12 and less IL-10 and are fully capable of priming T-cell responses [91]. In addition, metronomic or low-dose, non-myelotoxic administration of paclitaxel, doxorubicin, vincristine, and other drugs can cause activation and maturation of DCs, including increased IL-12 secretion, a critical factor required for T-cell priming. Signaling via STAT4 and Rho GTPases may account for these effects [92]. The third mechanism by which chemotherapy achieves immunomodulation is through suppression of immune inhibitory cells. For instance, oral administration of metronomic cyclophosphamide was shown to induce a profound and selective reduction of circulating $CD4^+CD25^+$ regulatory T cells and restored T and NK effector functions in end-stage cancer patients [93]. Cyclophosphamide may also have additional effects contributing to restoration of

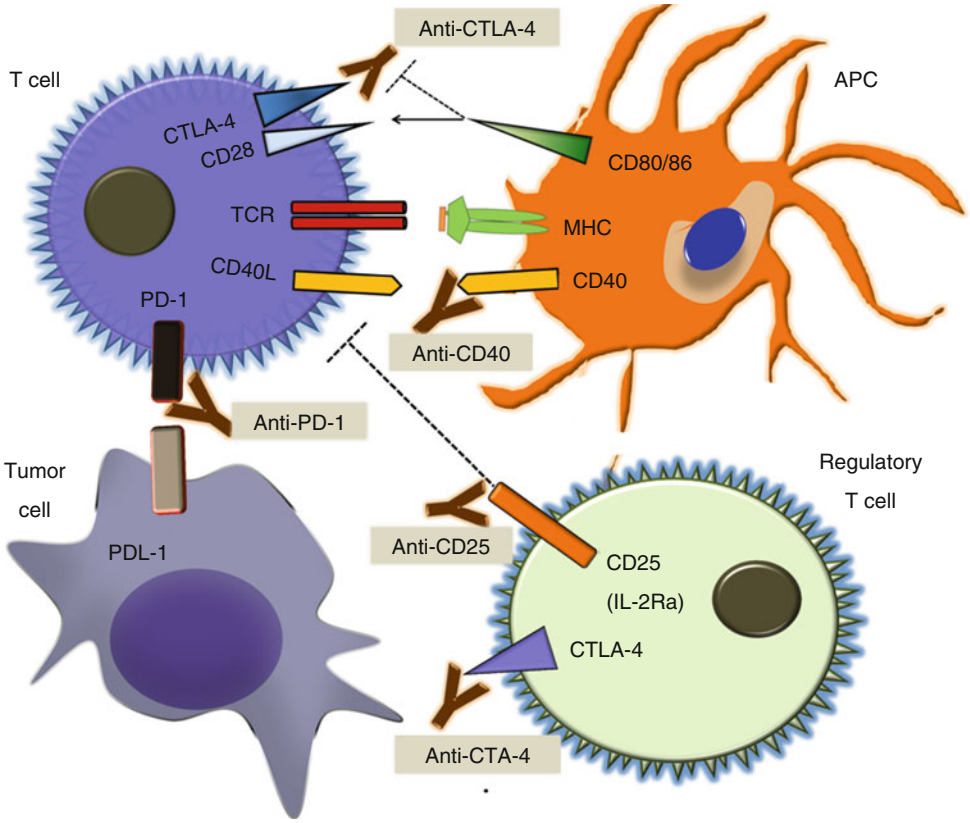

Fig. 29.1 Modulation of immune checkpoints can lead to improved therapeutic efficacy of vaccines or adoptively transferred T cells

the immune response; it can enhance IFN-γ production by splenocytes in a mouse model [94]. Conventional paclitaxel therapy also caused a significant decline in both numbers and activity of Treg, enhancing $CD4^+$ and $CD8^+$ activity systemically in patients with non-small cell lung cancer [95]. The mechanisms behind each of these immunomodulatory mechanisms are quite complex, and our understanding is still in its infancy. But effects appear to be dependent on drug type, dose, and schedule as well as the immune cell type.

Pleiotropic immune activation can also be achieved with cytokines and Toll-like receptor agonist therapy. Type I and II interferons and IL-2 are the most extensively studied cytokines for tumor therapy.

IFN-γ has been shown to have direct antiproliferative activity on ovarian cancer cells in vitro, which proved to be synergistic with cisplatin and doxorubicin [96–98]. In vitro and in vivo, IFN-γ upregulates HLA class I and class II molecules and antigen presentation in ovarian tumor cells [99], a requisite for recognition by T cells. In fact, HLA class I expression by the tumor correlates with the intensity of T-cell infiltration [100], a predictor of longer survival. Furthermore, IFN-γ has antiangiogenic effects [101].

Interleukin-2 (IL-2) promotes expansion and enhances the cytotoxicity of effector immune cells [102]. In addition, IL-2 can restore T-cell function following suppression by negative regulatory receptors such as PD-1 (see below). Because ovarian cancer patients exhibit spontaneous antitumor immune response, IL-2 therapy may be a rational approach to activate preexisting immunity or enhance immunomodulatory therapy. Intraperitoneal IL-2 was used in a phase I/II study in 41 patients with laparotomy-confirmed persistent or recurrent ovarian cancer. Weekly IL-2 infusion of 24 h duration was relatively well tolerated and demonstrated evidence of long-term efficacy in a modest number of patients. The toxicities of systemic IL-2 are significant; however, the peritoneal delivery method appeared to reduce the number and severity of the toxicities until the concentration in the intraperitoneal infusion reached the point where serum IL-2 became detectable. The appearance of systemic toxicity such as hypotension and thrombocytopenia, as well as locoregional dose-limiting toxicity (catheter infection), was associated with the highest doses. Twenty percent of patients had a negative third look, i.e., exhibited pathologic evidence of complete response and no residual disease at repeat abdominal exploration [29]. Recently, the therapeutic potential of several additional cytokines has been of increasing interest. IL-7, IL-15, IL-18, and IL-21 provide possible alternatives to IL-2. However, their function and clinical use are still under investigation [103–112].

Like cytokines, TLR agonists have multifaceted stimulatory effects on the immune system. TLR triggering induces DC maturation, which leads to the upregulation of costimulatory molecules, including CD40, CD80, and CD86, and secretion of immunomodulatory cytokines and chemokines. In

addition, TLRs can directly stimulate the proliferation of $CD4^+$ and $CD8^+$ T cells as well as reverse the suppressive function of Treg cells [113–115]. Several clinical trials have demonstrated that administration of agonists for TLRs 3, 4, 7, and 9 can enhance activity of cancer vaccines in the context of non-small cell lung cancer [116], non-Hodgkins lymphoma [117, 118], glioblastoma [119], superficial basal cell carcinoma [120], and melanoma [121–124]. Adding TLR 3, 4, 7, or 9 ligands was shown to activate $CD8^+$ cytotoxic T cells with increased IFN-alpha production and promote a stimulatory cytokine milieu at the tumor microenvironment [125, 126].

The use of antibodies to block T-cell inhibitory receptors such as CTLA-4 and PD-1 can lead to sustained activation and proliferation of tumor-specific T cells, preventing anergy or exhaustion and thereby allowing the development of an effective tumor-specific immune response. The majority of clinical data to date have emerged from studies in patients with melanoma [127], where CTLA-4 blockade has yielded objective responses. In a small study of ovarian cancer patients, one patient experienced a durable objective radiographic response. Multiple infusions of anti-CTLA-4 antibody every 3–5 months maintained disease control over 4 years [31]. The toxicities of CTLA-4 treatment showed similar pattern compared with those shown in melanoma patients, namely, grade I, rash in most of the patients (8/9); grade I or II, constitutional symptoms in 33 % (3/9) and sweet's syndrome in 22 % (1/9); and grade III, diarrhea in 22 % of the patients(2/9). Tumor regression correlated with the $CD8^+$/Treg ratio, suggesting that other forms of therapy that target Treg depletion may provide a highly effective form of treatment when combined with the tumor vaccine and CTLA-4 antibody arsenal [31].

Another way to enhance antitumor T-cell activity is through blockade of the PD-1 pathway. PD-1, expressed on activated T cells, binds PD-L1 and PD-L2 ligands. PD-L2 is restricted to professional antigen-presenting cells, while PD-L1 is expressed on many tissues. Importantly, ovarian carcinoma cells as well as tumor-infiltrating tolerogenic DCs and myeloid-derived suppressor cells express PD-L1 [128, 129], and expression levels correlate with disease course. Constitutive expression of PD-L1 by tumors conferred resistance to immunotherapy in mice [130], while antibodies blocking PD-L1 or PD-1 profoundly enhanced the efficacy of immunotherapy [130, 131]. A phase I study using PD-1 blocking antibody showed the antibody to be safe and well tolerated in patients with hematologic malignancies. Clinical benefit was observed in 33 % of the patients, with one complete remission [132].

Antibodies targeting the IL-2 receptor alpha chain (also known as CD25) can be used to deplete Tregs. In mouse models, the use of anti-CD25 monoclonal antibody before vaccination led to complete tumor rejection and establishment of long-lasting tumor immunity with no autoimmune complications [133, 134]. Daclizumab, which is an FDA-approved humanized IgG1-kappa mAb that binds specifically to CD25 [135], has been used in autoimmune disorders [136, 137], acute graft-versus-host disease [138], and in cancer patients with $CD25^+$ T-cell malignancies [139]. The advantage of daclizumab is that it is well tolerated and has a half-life of 20 days [140]. In a recent study, daclizumab was used in a single dose of 1 mg/m^2 prior to hTERT peptide vaccine for metastatic breast cancer. Total $CD4^+CD25^+$ and $CD4^+CD25^+FoxP3^+$ cells remained suppressed for several weeks after a single infusion. Importantly, administration of anti-CD25 antibody was compatible with effective vaccination [141].

The main mechanism of immune stimulation by CD40 agonists (including recombinant CD40 ligand and agonistic anti-CD40 antibodies) is activation of CD40-expressing DCs, resulting in increased survival, upregulation of costimulatory molecules, and secretion of critical cytokines for T-cell priming, such as IL-12. In vitro human cell studies have also been conducted to evaluate whether recombinant CD40L is able to stimulate maturation of DCs derived from ovarian cancer patients. In one study, autologous DCs from ten ovarian cancer patients were pulsed with killed primary tumors as a source of tumor antigens. DCs were then cultured in the presence of TNF, TRANCE (tumor necrosis factor-related activation-induced cytokine), and CD40L to induce maturation. These mature whole lysate-pulsed DCs were able to stimulate $CD8^+$ T cells that secreted IFN-γ in responses to ovarian tumor antigens. Similar results were also obtained in another study where DCs derived from ovarian cancer patients who were in remission were first loaded with HOCl-SKOV-3 tumor lysate and subsequently matured with activating anti-CD40 antibody [142]. In this study, mature DCs were able to stimulate both $CD8^+$ and $CD4^+$ antitumor T-cell responses. All these results highly suggested a potential benefit of using CD40L or anti-CD40 activating antibody as an adjuvant in DC-based whole tumor cell immunotherapy. Additional value of administering CD40 agonists in vivo is provided by the fact that ovarian cancers, like many tumors, express the CD40 receptor [143–146] and respond to CD40 ligation with apoptosis and growth inhibition in vitro and in vivo [145, 147, 148].

Cons

The usefulness of IL-2, although FDA approved for treatment of melanoma and renal cell carcinoma, has several limitations. Alone or in the context of adoptive immunotherapy, IL-2 is used at MTD, which induces a systemic inflammatory response with significant morbidity including multiple organ toxicities, most significantly the heart, lungs, kidneys, and central nervous system. Another manifestation of IL-2 toxicity is capillary leak syndrome, resulting in a hypovolemic state and fluid accumulation in the extravascular space [149]. Additionally, IL-2 is essential for the

peripheral homeostasis of $CD4^+CD25^+Foxp3^+$ Treg cells, and it is now known that IL-2 is also an important activator of Treg suppressive activity in vivo [150].

Many clinical trials have demonstrated the efficacy of type I interferon therapy in the treatment of hematologic malignancies [151–153], melanoma [154–158], and renal cell carcinoma [159–161]. In contrast, trials in ovarian carcinoma were less encouraging. Intraperitoneal recombinant IFN-α alone or combined with cisplatin as salvage therapy for persistent ovarian cancer after primary chemotherapy has shown clinical efficacy in small volume disease [162, 163], but there was no significant effect in a cohort of patients with recurrent, platinum-resistant disease [164]. A large randomized, phase III trial ($n=300$) conducted in patients with epithelial ovarian cancer concluded that INF-a2a as maintenance therapy following surgery and/or chemotherapy is not effective alone [165].

Conflicting results from trials involving IFN-γ administration highlight the difficulty in designing immunomodulation therapies. In one instance, a threefold prolongation of progression-free survival was observed in a phase III multicenter study from Europe with subcutaneous administration of rhIFN-γ combined with MTD cisplatin and cyclophosphamide chemotherapy, with minimal added toxicity [166]. However, in a subsequent randomized phase III trial conducted in the USA, addition of subcutaneous rhIFN-γ to carboplatin and paclitaxel did not improve survival [167]. Although one cannot exclude that racial and other demographic differences may account for opposite results, these data may indicate that the choice of chemotherapy drugs is in fact critical in combinatorial approaches with immunotherapy. Indeed, whereas cyclophosphamide has potent immunomodulatory effects on suppressive Tregs, high-dose steroids, which are necessarily given with paclitaxel to prevent acute hypersensitivity reactions, are immunosuppressive and induce Treg in the setting of antigen presentation.

Similarly, the use of TLR agonists in the clinic requires careful preclinical evaluation. For example, in the absence of specific cell-mediated antitumor immunity, nonspecific activation of inflammation might in fact promote tumor growth rather than reducing it [168]. TLR4 agonists were shown to promote tumor cell survival, tumor growth, and paclitaxel resistance in a proportion of ovarian cancer cells [169, 170].

Meanwhile, agonistic anti-CD40 antibody is best used in combination with vaccines or TLR agonists [171, 172]. This is because, when used alone, it can accelerate the deletion of tumor-specific cytotoxic lymphocytes [173].

Conclusions

In the past decade, we have witnessed important advances in the development of immunotherapies for gynecologic cancers. First, ovarian cancers are now seen as potentially immunogenic tumors, a characterization formerly reserved only for melanoma and renal cell cancer. Second, the a priori notion that chemotherapy drugs antagonize immune mechanisms altogether was challenged by evidence that select chemotherapy drugs commonly used to treat gynecologic cancers have important immunomodulatory effects. This has opened the door to explore interactions of these drugs with natural antitumor immunity. Third, several mechanisms of tumor immune escape, accounting for failure of immunotherapy, have been deciphered, and the importance of combinatorial immunotherapy targeting both adaptive and innate effector and suppressor mechanisms has been proven. Fourth, this decade has produced novel and potent *bona fide* stimulants of innate and adaptive immunity. The next decade will be the time to test and optimize these combinations to maximize efficacy and decrease toxicity. Rational combinations of agents will require understanding of their precise mechanism of action in order to select combinations yielding positive interactions.

Future Directions

Evidence now convincingly shows that ovarian cancers are immunogenic tumors. The dramatic advances in laboratory technology and clinical procedures in cellular immunotherapy, along with the development of powerful immunomodulatory antibodies, create new opportunities in ovarian cancer therapeutics. The challenge for the next decade will be to test rational combinations that offer maximal clinical benefit at the lowest cost.

Selection of appropriate patients for clinical trial participation will also be quite influential. Additional biomarkers are needed to maximize selection of patients who may benefit from immunotherapy. Evidence to date indicates that many ovarian cancer patients display a spontaneous antitumor immune response. These patients may be best suited for vaccine therapy or TIL-based therapy as they are the most likely to harbor a natural repertoire of tumor-reactive T cells with tumor rejecting potential that can be expanded in vivo or ex vivo. In addition, patients whose tumors exhibit intraepithelial T cells may be most likely to respond to immunotherapy as the tumor microenvironment is already conducive to T-cell homing and engraftment. Finally, more work will be necessary to develop strategies to integrate immunotherapy with current standard of care. We have previously demonstrated that patients with advanced ovarian cancer whose tumors exhibit low frequency of intraepithelial $CD8^+$ T cells or high Ki67 expression are more likely to draw benefit from aggressive surgical cytoreduction, while debulking did not significantly affect the survival of patients with brisk $CD8^+$ T cells or low Ki67 expression [17]. It is possible that immunotherapy with adoptive transfer of TILs and/or vaccine plus immunomodulation could be a rational

adjuvant therapy for patients with intraepithelial T cells following conventional debulking surgery and chemotherapy. Based on the observation that VEGF antibody blockade enhances T-cell infiltration in tumors and that its efficacy depends on antitumor CD8 T-cell response [174], it is possible that patients with intraepithelial T cells may also respond better to bevacizumab or other VEGF inhibitors. On the other hand, our data suggest that maximal debulking efforts should be undertaken in tumors with low T cells and it is possible that these patients are not the best candidates for adjuvant immunotherapy that exploits natural antitumor immune response. Personalized adoptive therapy with engineered T cells redirected against known tumor epitopes might be the most efficient approach to adjuvant immunotherapy in patients with low level of naturally occurring TILs. Careful preclinical evaluation in well-characterized animal models will be necessary to evaluate combinations before undertaking clinical studies. However, the major challenge facing the field at present is to conduct randomized clinical trials demonstrating sufficient clinical benefit to justify the logistics and expense of customized cellular therapies. A positive outcome from immunotherapy trials in terms of effective therapy, extension of progression free, and overall survival would represent a major advancement for patients with advanced ovarian cancer.

Concluding Comments

- Appropriate diagnostic methods are needed to identify patients suitable for immunotherapy.
- Novel pharmacodynamics biomarkers need to be implemented to provide proper metrics for effectiveness of immune therapies.
- New strategies need to be developed to integrate immunotherapy with standard of care or targeted therapies to offer long-term and durable benefit.
- Formulation of effective, scalable, and reproducibly manufactured vaccines, T-cell products and immunomodulatory agents will be necessary to make these therapies commercially viable.
- Randomized clinical trials need to be conducted to demonstrate sufficient clinical benefit in order to justify the expense of immunotherapies and the integration of them into standard of care.

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