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Dx/Rx

Dx/Rx: Gynecologic Cancer

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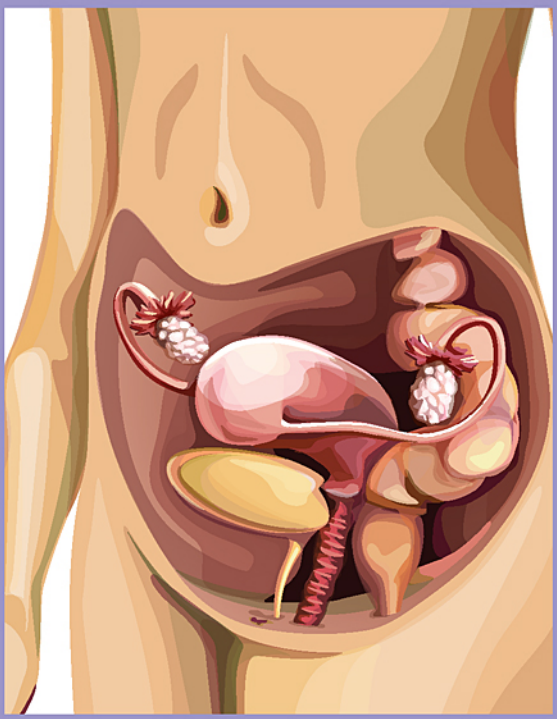

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Dx/Rx:
Gynecologic Cancer

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Dedications

I am grateful to Susana for agreeing to undertake this huge endeavor and to the folks at Jones and Bartlett (especially Chris Davis) for this opportunity. Once more, I am indebted to my parents, Mody and Inday Dizon, for their love and encouragement. I dedicate this book to my family: my sisters, Michelle, Mae, Precy, and Marie; my spouse, Henry; and our kids, Isabelle, Harrison, and Sophia. I also dedicate this book to my mother-in-law, Marilyn, who helps run our hectic household and allowed me to finish this book, and to Nick Hemond, who I hope, as an intern in women's oncology, will find inspiration and promise in what he witnesses to help him realize that we can always do more. Finally, it is dedicated to the women, cancer survivors all, who have allowed me to participate in their care and welcomed me into their lives, amidst some of the most trying times. I hope I have served you well, because you have always been the source of my continued passion as we strive for a cure to these tumors.

Don S. Dizon, MD, FACP

I dedicate this book to my parents, Maria and Humberto Campos, who had the wisdom to understand that the future lies in the education of the young and old. As immigrants to this country, their focus was one that centered on hard work and commitment to education. In addition, this book is dedicated to the patients who continue to educate their healthcare providers on the need for better therapeutics that effectively balance treatment with quality of life. I am indebted to my colleague Don Dizon who continues to share with me innovative projects aimed at moving the field of gynecological cancers forward. It is our goal that this text will ignite the same passion in others pursuing the ultimate goal: a cure for patients with gynecological malignancies.

Susana M. Campos, MD, MPH

Contents

Foreword

The tides have changed. In the past several years there has been considerable interest, and hence, progress in the prevention, diagnosis, surgical management, and treatment of gynecological malignancies. Basic diagnostic tools and therapeutics have been replaced by provocative and innovative measures that allow a personalized approach to patient management.

An understanding of cellular signaling pathways involved in carcinogenesis and tumor growth have allowed the development of prevention strategies and the development of targeted cancer drugs. To this end, various targeted therapeutics have been recently explored in the management of gynecological cancers. These include monoclonal antibodies to epidermal growth factor receptors (EGFR), small molecule tyrosine kinase inhibitors, monoclonal antibodies directed at the vascular endothelial growth factor (bevacizumab), and the small tyrosine kinase inhibitors that target the vascular endothelial growth factor receptor. In addition, several other agents have come forth as potential therapeutic agents in the management of ovarian cancer. These include monoclonal antibodies to the folate receptor, triple angiokinase inhibitors, PARP inhibitors, aurora kinase inhibitors, inhibitors of the Hedgehog pathway, folate receptor antagonists, and MTOR inhibitors.

The introduction of novel therapeutics has been paralleled by successes in other disciplines involved in the treatment of gynecologic cancers. Continuing with a movement towards minimally invasive procedures, robotic surgical systems are finding a place in the standard armamentarium for the surgical gynecologic oncologist. Data is already available indicating it is not only comparable to both laparoscopic and open surgery, but also allows for less postoperative

complications and potential morbidity. Likewise, the utility of intensity modulated radiation therapy continues to develop in the management of certain gynecological malignancies.

At the forefront is research centered on the prevention of gynecological cancers. Advances in the understanding of the epidemiology of cervical cancer coupled with innovative tools have produced the HPV vaccine, a therapeutic capable of the prevention of significant morbidity and mortality in women. It is hopeful that novel approaches, potentially relying on genomics and proteomics, may lead to the development and validation of a protein-based signature for the detection of ovarian cancer.

This volume brings together an emphasis in the multidisciplinary focus that is required to effectively manage these diseases. Experts in the field of gynecologic cancer have collaborated in this text in order to increase the understanding of new treatment paradigms in women's pelvic malignancies, and to increase knowledge of new technologies and procedures to stimulate interest in and improve care of women with gynecologic cancers.

Our continued success lies in our commitment to the development and participation in clinical trials. Only then will we walk forward…

Susana M. Campos, MD, MPH
Don Dizon, MD, FACP

Editor's Preface

I would like to welcome you to the DX/RX Oncology Series, and in particular to this volume, DX/RX: Gynecologic Cancer, which focuses on the diagnosis and management of a large and diverse group of malignancies including ovarian epithelial cancers, germ cell tumors, endrometrial cancer, cervival cancer, and many more. The management of these diseases encompasses coordinated efforts from gynecological surgical oncology, radiation oncology, and medical oncology. As with all volumes in this series, this comprehensive handbook is organized and presented in an easy-to-read, succinct bulleted format with summary tables. The management is organized practically into early and advanced disease settings, with discussion of novel targeted therapies as well. Drs. Dizon and Campos have put together a remarkably easy to grasp, comprehensive overview of the management of gynecologic malignancies. You will not be disappointed—there truly is "something for everyone" in this volume of the DX/RX Oncology Series.

Manish A. Shah, MD

SECTION 1

Cancers of the Ovary

CHAPTER 1

Epithelial Ovarian Cancer

Epidemiology[1]

- Accounts for nearly 3% of all cancers among women
- Over 20,000 new cases are diagnosed each year in the United States
  - Of all the gynecologic neoplasms, it is associated with the highest mortality rate of any gynecologic cancer: Over 5,000 women die of this disease annually.
- Risk increases with age and peaks in the late 70s
- Approximately 81% of cases are diagnosed with advanced (stage III/IV) disease
- Incidence higher among the Caucasian population (17.9/100,000) versus African American population (11.9/100,000)
- Distinct geographic variations with the highest incidence in industrialized countries; Japan a notable exception (3.0/100,000)
- Overall 5-year survival rate is 45%
- 30% in patients with distant disease at diagnosis

Ovarian Cancer Risk Factors

- Factors associated with an increased risk:
  - Advanced age
  - Family history
  - Nulliparity
  - Estrogen replacement
  - Talc powder
  - Pelvic inflammatory disease
  - Living in industrialized Western countries
  - Being of Jewish descent

- Factors associated with a decreased risk:
  - Lactation
  - Oral contraceptives
  - Parity
  - Reproductive surgery (tubal ligation, oophorectomy/hysterectomy)
  - Diet high in carotene
  - Low alcohol use
  - Low lactose intake

Hereditary Ovarian Cancer

- Only 5% to 10% of cases
- Hereditary breast/ovarian cancer syndrome
  - BRCA1 and BRCA2 mutations
  - BRCA1 and BRCA2 classified as tumor suppressor genes that play a role in repair of oxidative damage to DNA
  - BRCA1 and BRCA2 located on chromosomes 17 and 13, respectively
  - Inheritance of these mutations confers an increased lifetime risk for ovarian cancer:
    - BRCA 1 = 20% to 60%
    - BRCA 2 = 10% to 35%

Signs and Symptoms

- Abdominal bloating
- Increased abdominal size
- Urinary symptoms
- Early satiety
- Changes in bowel habits
- Pelvic pain
- Nausea
- Shortness of breath
- Vaginal bleeding
- Abdominal nodules

Screening

- PLCO study (Prostate, Lung, Colorectal, and Ovarian Trial) examined the impact of screening patients with serum CA-125 levels and transvaginal ultrasound (TVUS)[2]
  - Among 34,000 women screened, the compliance was 83% at time 0 and 83% after the third round of screening
  - Transvaginal ultrasound screens that were positive declined during screening from 4.6 to 2.9 to 3.4; screening rates for cancer antigen 125 (CA-125) positivity remained constant
  - Of 80 ovarian cancers detected during four rounds of screening, 60 discovered during screening for a positive predictive value range between 1% and 1.3%
  - Majority of screened cases still advanced at diagnosis
  - Combining CA-125 to ultrasound: positive predictive value still only 23.5%
  - Not deemed an effective strategy for use in the general population
  - No technique is specific as a screening tool but continued research on serum proteomics is ongoing
- The United Kingdom Trial in Ovarian Cancer Screening (UK-TOCS) enrolled over 200,000 women between 2001 and 2005, who were randomized to no screening versus screening by CA-125 and transvaginal ultrasound (combined screening) versus transvaginal ultrasound alone.[3]
  - Compliance was improved with combined screening as compared to ultrasound alone, 99% versus 95%, respectively; combined screening was also associated with a lower chance that women would need to undergo a more intensive evaluation compared to screening by ultrasound alone (0.3% versus 3.9%, respectively)
  - Among women undergoing screening: 0.2% undergoing combined screening underwent surgery; 1.8% who underwent ultrasound alone had surgery

- Surgery picked up 87 primary cancers with 42 detected among women undergoing combined screening and 45 among those undergoing ultrasound alone; invasive ovarian cancer picked up by combined screening more often than on ultrasound with 33 and 25 cancers discovered, respectively. However, a significant number of cases were advanced at diagnosis.
- Still too early to determine if screening also improved survival in women ultimately diagnosed with ovarian cancer

Diagnosis

- Early diagnosis remains difficult as symptoms are nonspecific; however, a study from the University of California at Davis compared the symptoms of women over 65 who were ultimately diagnosed with ovarian cancer to symptoms in a matched cohort with breast cancer and a third group without a diagnosis of cancer.[4] The following were more common in women with ovarian cancer, and were present 1–3 months before diagnosis:
  - Abdominal pain (odds ratio [OR], 6.0; 95% confidence interval [CI], 5.1–6.9)
  - Gastrointestinal symptoms (OR 2.3; 95% CI, 1.8–3.0)
  - Pelvic pain (OR 4.3; 95% CI, 2.8–6.7)
- Consider these target symptoms—if persistent require workup to rule out this diagnosis
- Workup requires: physical and pelvic examination, CA-125, and pelvic imaging, including pelvic ultrasound or CT scan

Pathology

- Approximately 90% of all ovarian malignancies are of epithelial origin. Histologic subtypes include:
  - Papillary serous carcinoma
  - Clear cell
  - Mucinous carcinoma
  - Endometroid carcinoma
  - Carcinosarcoma

- Differentiation
  - Epithelial tumors are classified according to the degree of histological differentiation:
    - Grade 1 (well differentiated)
    - Grade 2 (moderately differentiated)
    - Grade 3 (poorly differentiated)

Staging of Ovarian Cancer

- Both peritoneal and ovarian cancers are clinically staged based on Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging system[5] (Table 1-1)

Table 1-1: Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) Staging System of Ovarian and Peritoneal Cancer[5]

Stage	Characteristics
I	Growth limited to the ovaries
IA	Growth limited to one ovary
IB	Growth limited to both ovaries
IC	Growth limited to one or both ovaries; capsule rupture; ascites containing malignant cells or positive peritoneal washings
II	Growth involving one or both ovaries with pelvic extension of disease
IIA	Extension of disease or metastases to the uterus and/or fallopian tubes
IIB	Extension of disease to other pelvic organs
IIC	Either IIA or IIB and capsule rupture; ascites containing malignant cells or positive peritoneal washings

(Continues)

Table 1-1: Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) Staging System of Ovarian and Peritoneal Cancer[5] (Continued)

Stage	Characteristics
III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; histologically verified malignant extension to the small bowel or omentum
IIIA	Tumor limited to the pelvis with negative nodes but with seeding of abdominal peritoneal surfaces
IIIB	Tumor of one of both ovaries; implants on the abdominal peritoneal surface, none <2 cm; nodes negative
IIIC	Abdominal implants >2 cm and/or positive retroperitoneal or inguinal nodes
IV	Growth involving both ovaries with distant metastases; positive pleural effusion or parenchymal liver metastases

  - Positive cytology for patients presenting with pleural effusion or cytologic confirmation of malignancy of hepatic or other visceral lesions required for stage IV diagnosis
- Fallopian tube cancers are treated as ovarian cancers. The staging system for these tumors is also based on the FIGO staging system.[6] (Table 1-2)

Treatment

- Surgical debulking is first treatment modality for the vast majority of women
- Proper surgery involves total hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO), omentectomy, and cytology from pelvic washings

Table 1-2: FIGO Staging of Cancers of the Fallopian Tube

Stage	Characteristics
I	Tumor limited to the fallopian tube
IA	Tumor limited to one tube without serosal penetration; no ascites
IB	Tumor limited to both tubes, without serosal penetration; no ascites
IC	Tumor limited to one or both tubes +/− extension to or through the serosa or with positive ascites or peritoneal fluid washings
II	Tumor involves one or both tubes with pelvic extension
IIA	Extension and/or metastases to the uterus and/or ovaries
IIB	Extension of disease to other pelvic structures
IIC	Pelvic extension with ascites containing malignant cells or positive peritoneal washings
III	Tumor involving one or both fallopian tubes with peritoneal implants outside the pelvis
IIIA	Microscopic peritoneal implants outside the pelvis
IIIB	Macroscopic implants outside the pelvis, 2 cm or less in greatest dimension
IIIC	Macroscopic implants outside the pelvis, over 2 cm in greatest dimension and/or regional lymph node metastases
IV	Distant metastases. For stage IV, liver parenchymal involvement must be identified; if pleural effusion, positive cytology must be demonstrated.

- In absence of gross disease, random biopsies of the abdomen and pelvic cavities, node dissection or samplings, and diaphragmatic biopsies also performed
- Chemotherapy is the mainstay for postoperative treatment and is recommended for both early and late disease; carboplatin and paclitaxel are current standard agents considered in ovarian cancer
- Gynecologic Oncology Group (GOG) is the U.S. cooperative group mechanism for clinical trials in ovarian cancer

Early Stage Ovarian Cancer

- GOG 157 was a study of three versus six cycles of adjuvant carboplatin (C) and paclitaxel (P) in surgically staged patients with stage IA grade 3, stage IB grade 3, clear cell, all stage IC, and stage II epithelial ovarian cancer (EOC)[7]
  - The recurrence rate for six cycles was 24% lower (hazard ratio [HR]: 0.761; 95% CI, 0.51 to 1.13, p = 0.18), and the estimated probability of recurrence within 5 years was 20.1% (six cycles) versus 25.4% (three cycles); overall death rate was similar for these regimens (HR: 1.02; 95% CI: 0.662 to 1.57)
  - Although a trend to improved outcomes was seen with further treatment, it was not significant; most, however, consider six cycles to be standard of care, particularly in curative setting
- GOG 175 was follow-up trial to GOG 157; women with early ovarian cancer were randomized to three cycles of carboplatin and paclitaxel followed by observation or consolidation with weekly pacitaxel at 40 mg/m2[8]; study closed in 2006; survival results not yet given
- Two trials in early ovarian cancer also performed in Europe; the first was International Collaborative Ovarian Neoplasm trial (ICON-1), second was Adjuvant Chemotherapy in Ovarian Neoplasm trial (ACTION)[9,10]; eligibility was more specifically detailed in the ACTION trial—patients had to undergo surgical attempt and patient entry was limited to women with high-risk early

stage disease (stages IA/B with grade 1 or 2 tumors, stage IC or IIA, or diagnosis of clear cell). ICON-1 alternatively defined eligible patient based on physician discretion that one needed chemotherapy. Results were published as a combined analysis and showed:

- After a median follow-up of over 4 years, 245 patients died or had a recurrence (ICON1: 133, ACTION: 112)
- Overall survival at 5 years was 82% in the chemotherapy arm and 74% in the observation arm (HR = 0.67, 95% CI = 0.50 to 0.90)
- Recurrence-free survival at 5 years supported the use of adjuvant chemotherapy versus observation (76% versus 65%; HR = 0.64, 95% CI = 0.50 to 0.82)
- Subgroup analysis was performed in the ACTION trial, where the extent of surgical staging was evaluated.[10] In women who had a complete surgical staging, chemotherapy did not improve outcomes, however, in those deemed not to have undergone a complete surgical procedure, adjuvant chemotherapy was associated with an improvement in both disease-free and overall survival.

Advanced Stage Ovarian Cancer

- Primary cytoreductive surgery by a gynecologic oncologist remains the standard of care in advanced ovarian cancer
- Bristow et al. performed a meta-analysis evaluating the impact of surgical cytoreduction in the context of adjuvant platinum-based treatment, which included data on 6,885 patients with stage III–IV disease[11]
  - Each 10% increase in maximal effort to reduce the volume of disease with surgery was associated with a mean increase in survival time of 5.5%
  - Cohorts with a maximum surgical effort resulting in no greater than 25% cytoreduction had a mean weighted survival time of 23 months; those whose surgical cytoreduction was above 75% was 34 months

- Current efforts are evaluating the impact of extending surgical debulking to include liver resection and upper abdominal disease resection remains under investigation
  - Chi et al. published observational data suggesting optimal surgery including resection of disease involving the upper abdomen (traditionally considered suboptimally resected) greatly improves progression-free survival (PFS) and overall survival (OS)[12]

Neoadjuvant Chemotherapy

- Use of primary chemotherapy with interval debulking also has been considered
  - European Organization for Research and Treatment of Cancer-Gynecological Cancer Group (EORTC-GCG) randomized 319 patients deemed not surgical candidates (for an optimal cytoreduction) to three cycles of cisplatin-cyclophosphamide followed by reassessment; women who seemed to benefit randomized to surgery (interval cytoreduction) followed by three cycles of further treatment versus completion to six cycles of chemotherapy (no surgery)[13]
    - Interval surgery was associated with a 33% reduction in the risk of death (95% CI, 10%–50%) at 2 years with significant benefits in both PFS ($p = 0.01$) and OS ($p = 0.01$)
  - GOG conducted a confirmatory trial in which all patients underwent an initial attempt at surgical debulking by trained gynecologic oncologists; those unable to be maximally cytoreduced at that time were randomized to a trial of three cycles of cisplatin/paclitaxel followed by interval surgery and three adjuvant cycles versus completion of chemotherapy to a total of six cycles (no surgery)[14]
    - Study enrolled 296 women and found no benefit to interval surgery compared to chemotherapy alone without further surgery in terms of both PFS (HR 1.07, 95% CI, 0.87–1.31) or risk of death (Relative risk [RR] 0.99, 95% CI, 0.79–1.24)

- At the 2008 International Gynecologic Cancer Society meeting in Bangkok, Ignace Vergote presented findings from EORTC-GCG trial, conducted with the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG); patients were randomized to primary surgery followed by six cycles of adjuvant platinum-based chemotherapy versus six courses of chemotherapy with interval debulking after first three courses[15]
  - Eligibility included patients with biopsy-proven disease or at least a fine needle aspirate (FNA) suggesting primary ovarian cancer; at least 2 cm of disease outside the pelvis, and a CA-125/CEA ratio over or equal to 25
  - Similar outcomes in both PFS (HR 0.99, 95% CI, 0.87–1.13) and OS (HR 0.98, 95% CI, 0.85–1.14) seen in each arm

Adjuvant Therapy: Intravenous Treatment

- Several key trials have established platinum/paclitaxel as the standard of care combination
- GOG 111 was the first randomized trial comparing cisplatin with cyclophosphamide (CC) to cisplatin with paclitaxel (CP) in women with suboptimally resected advanced ovarian cancer (stages III–IV)[16]
  - Addition of paclitaxel to cisplatin, when compared to CC, associated with improvements in overall response rates (73% versus 60%, respectively, $p = 0.01$), time to progression (18 versus 13 months, $p < .001$), and median OS (38 versus 24 months, $p < .001$)
- Results were confirmed in a second GOG trial that compared cisplatin-based therapy (either in combination with paclitaxel or as a single agent) to single-agent paclitaxel (GOG 132)[17]
  - Study showed paclitaxel was a less-effective agent than either cisplatin arm showing a lower response rate (46% versus 74% with single-agent cisplatin and 72% with combination)

  - No survival advantage was seen (median PFS 16.4 versus 11.4 versus 14.1 months; median OS 30 versus 26 versus 26.6 months), but study was notable for significant crossover; those treated on the cisplatin arm went on to receive paclitaxel and vice versa; study therefore suggests that sequential treatment may be equivalent when using these agents
- Given the toxicity of cisplatin, investigators then sought to determine if carboplatin (which causes far less neuropathy, renal dysfunction, and less nausea) would be equivalent to cisplatin in GOG 158[18]
  - In both arms, paclitaxel was used and patients randomized to either platinum salt
  - The two drugs were shown to be equivalent, heralding the use of carboplatin as the standard agent for ovarian cancer
- Most recently reported adjuvant trial is GOG 182[19]; study was a five-arm trial evaluating whether standard second-line agents (topotecan, pegylated liposomal doxorubicin [PLD], gemcitabine) would improve survival outcomes when combined with carboplatin and paclitaxel
  - Ultimate findings: when compared to standard paclitaxel and carboplatin, the addition of a third cytotoxic agent provided no benefit in PFS or OS after optimal or suboptimal cytoreduction
- Current efforts are evaluating the role of biologic agents and their ability to improve survival; GOG 218 randomized patients to carboplatin and paclitaxel with or without bevacizumab, with a second randomization to extended treatment with bevacizumab or placebo[20]; a similar trial, ICON-7, is ongoing in Europe[21]

Intraperitoneal Chemotherapy

- Given the propensity of ovarian cancer to spread within the peritoneal cavity, investigators have long evaluated the effect of locoregional therapy as a strategy with the use of intraperitoneal therapy; multiple trials have been

published and results of seminal studies are reviewed in Table 1-3[22–28]

- GOG 172 was the last randomized intraperitoneal (IP) versus intravenous (IV) chemotherapy trial published; women with optimally cytoreduced (defined as volume of disease following surgery of no more than 1cm) ovarian, fallopian tube, or peritoneal cancers submitted to an experimental regimen of IV paclitaxel

Table 1-3: Upfront Randomized Trials of Intravenous (IV) Versus Intraperitoneal (IP) Chemotherapy in Optimally Cytoreduced Ovarian Cancer

Study	Arms	N	Survival Outcome
Kirmani[21]	IP CDDP-VP16 IV CDDP/CTX	61	No difference in OS at 46 months.
GOG 104[22]	IV CTX/IP CDDP IV CTX/CDDP	546	OS favored IP Arm (HR 0.76, 95% CI 0.61–0.96)
Polyzos[23]	IV CTX/IP CBDCA IV CTX/CBDCA	90	No difference in OS (26 vs. 25 months)
GONO[24]	IV CTX/EDox+IP CDD P IV CTX/ EDox/CDDP	113	No difference in OS (67 vs. 51 months, p = 0.14)
Yen[25]	IP CDDP IV CDDP	132	OS: 48 vs. 43 months (NS)
GOG 114[26]	IV CBDCA x2 then IP CDDP/IV Pac IV CDDP/Pac	462	OS: 63 vs. 52 months (p = 0.05) PFS: 28 vs. 22 months (p = 0.01)
GOG 172[27]	IV Pac D1/IP CDDP D2, IP Pac D8 IV CDDP/Pac	415	OS: 66 vs. 50 months (p = 0.03)

IP: intraperitoneal; IV: intravenous; CDDP: cisplatin; VP-16: etoposide; CTX: cyclophosphamide; CBDCA: carboplatin; EDox: epidoxorubicin; Pac: paclitaxel.

135 mg/m^2 on day 1, IP cisplatin 100 mg/m^2 on day 2, and IP paclitaxel 60 mg/m^2 on day 8, or standard treatment using IV paclitaxel 135 mg/m^2 on day 1 and IV cisplatin 75 mg/m^2 on day 2[28]
  - Complete pathologic responses (defined as negative pathologic findings identified during second-look surgery) higher in women treated on the experimental program (57% versus 41%, respectively)
  - Both PFS (24 versus 18 months, respectively, $p = 0.05$) and OS prolonged (66 versus 50 months, respectively, $p = 0.03$)
  - Quality-of-life assessments showed that while the IP arm was more difficult, 12 months after treatment quality of life between the arms was similar
- A Cochrane review of the randomized trials looking at IP treatment has been performed and demonstrated that IP therapy resulted in a longer disease-free interval (HR 0.79; 95% CI 0.69 to 0.90). In addition, women treated with IP were also 20% less likely to die of their disease (HR 0.79; 95% CI 0.70 to 0.90).[29]

Consolidation Therapy

- Almost 75% of the patients who achieve a clinical complete response and 50% of those who obtain a pathological response will relapse after a median time of 18–24 months.
  - Given the observation that most patients respond well to first-line chemotherapy but subsequently recur, many investigators interested in supplementing primary therapy treatment
  - Prolonged administration of first-line agents or continuation of either carboplatin or paclitaxel has been looked at.[30–33] However, none of these strategies have prolonged survival in the adjuvant setting. These are summarized in Table 1-4.
- GOG 178 the most recent experience with consolidation treatment published; patients who entered a clinical complete response after standard platinum/taxane

Table 1-4: Extended Chemotherapy Trials in Ovarian Cancer

Study	N	Regimen	Randomization	Main Outcome	Comments
Hakes et al.[29]	78	CDDP + Dox + CTX	5 versus 10 cycles	5 year OS: 29% vs. 36% (p = NS)	ORR 34% vs. 32%
Danish Ovarian Study Group[30]	202	CDDP + Dox + CTX	6 versus 12 cycles	3 year OS: 29% vs. 35%	pCR: 23% vs. 25%
North Thames Ovary Study Group[31]	225	Consolidation CBDCA	5 versus 8 cycles	Median OS: 24 months in both arms	
GOG 178[32]	262	Consolidation Paclitaxel	3 versus 12 months	Median PFS: 21 vs. 28 months. p = 0.0023	No Difference in OS

containing treatment were randomized to 3 versus 12 months of continued paclitaxel chemotherapy[33]
  - Continued treatment with 12 months of paclitaxel associated with a 7-month gain in PFS over a 3-month course
  - No OS advantage noted with either treatment
- The use of alternative agents has been proposed as an option as well, given that resistance to platinum is the primary cause of treatment failures in ovarian cancer.
  - Alberts et al. evaluated oral altretamine in a phase II trial in women with stage III ovarian cancer who had achieved remission.[34] At a median follow-up of 6.2 years, 97 of 112 participants were evaluable for efficacy endpoints. The median PFS was 28 months for the entire cohort; for optimally resected patients, it was 45 months, which was longer than that of those suboptimally resected at 17 months. The proportion remaining disease free was 43% in the optimal cohort and 14% in the suboptimal cohort.
  - DePlacido et al. conducted the MITO-1 (Multicenter Italian Trials in Ovarian Cancer) trial, which evaluated topotecan versus no further treatment after adjuvant carboplatin and paclitaxel.[35] This trial enrolled 273 women with predominant stage III (65%) or IV (10%). Unfortunately, there was no difference in PFS noted, 18.2 months with topotecan versus 28.4 months in the control arm (HR 1.18; 95% CI 086,1.63).
  - Rocconi et al. evaluated pegylated liposomal doxorubicin (PLD) in this setting.[36] In this small study of 30 women, 79% were able to complete the planned four cycles of conslidation. The median PFS was 15 months with OS of 31 months. Four-year survival was achieved by 47%.
  - Several studies have reported on the use of radioisotope conjugated monoclonal antibodies, but a phase III trial that enrolled 844 patients evaluated a HMFG1 murine monoclonal antibody labeled with yttrium-90 given as an intraperitoneal treatment in women with

surgically defined complete remission.[37] At a median of 3.5 years of follow-up, there was no difference between time to relapse or survival associated with this treatment as a single-dose administration.

- Intraperitoneal (IP) chemotherapy as consolidation has also been explored as IP administration allows increased drug levels into the abdominal cavity, when compared to IV administration.
  - Barakat et al. conducted a trial of IP cisplatin and etoposide for three cycles versus observation in 82 patients, demonstrating a median PFS improvement with further treatment that was statistically significant ($p = 0.03$).[38]
  - Piccart et al. performed a similar trial of consolidation IP cisplatin versus observation in 66 patients.[39] There was no difference in 8-year PFS or OS seen over no further treatment.

Recurrent Disease

Serologic Relapse

- A special setting in women with ovarian cancer is the relapse solely on the basis of the CA-125; called serologic recurrence
- A sustained rise in CA-125 often predicts disease recurrence by signs or symptoms by about 5 months[40]; doubling of a prior value, confirmed by a second value at least 4 weeks apart, often used to detect relapse
- Early treatment based solely on CA-125 rises not recommended; results from the MRC 05 trial, presented at 2009 ASCO meeting, enrolled 1442 women who had entered a clinical complete remission following platinum-based therapy and who underwent serial CA-125 testing every 3 months but were blinded to the results.[40] Patients whose CA-125 became elevated to 2 times the upper limit of normal were then randomized to an early treatment arm, in which case the clinician and patient were informed of the CA-125 results, versus delayed

treatment, in which they were not informed and treatment was based on clinical indications being present. The study showed the following:

- At a median follow-up of 57 months, 529 patients (37%) of the enrolled cohort were ultimately randomized.
- Those randomized to early treatment started second-line therapy at a median of 0.8 months while those in the delayed arm started second-line treatment at a median of 5.6 months, $p < 0.00001$.
- Despite this, there was absolutely no difference in overall survival between the two arms (HR 1.0, 95% CI, 0.82, 1.22).
- Those starting treatment early did show an earlier decline in their global health score compared to the delayed treatment arm; the median time to deterioration was 3.1 versus 5.8 months, respectively, $p = 0.001$.

Definitions of Recurrence

- Despite gains in treatment, vast majority of women with ovarian cancer relapse; treatment of relapse has been segregated based on the duration a woman has had from prior platinum-based treatment; known as the platinum-free interval
  - Platinum sensitive: Recurrence of disease during or on completion of platinum chemotherapy after a treatment-free interval of 6 months or longer
  - Platinum refractory: Recurrence of disease during or on completion of platinum chemotherapy
  - Platinum resistant: Recurrence of disease on platinum chemotherapy after less than 6 months

Platinum-Sensitive Ovarian Cancer

- Women with platinum-sensitive relapse have both surgical and medical options for treatment; both should be considered seriously
- Surgery for relapse is termed secondary cytoreduction; data from surgical treatment of 153 women with

platinum-sensitive recurrence from Memorial-Sloan Kettering Cancer Center reported[41]

- In this series: 41% underwent successful surgery to no residual disease and a total of 52% were cytoreduced to less than 0.5 cm or residual disease (i.e., an optimal resection); indicating that with appropriate selection a significant proportion can have a successful cytoreduction
- Those able to undergo an optimal cytoreduction had median OS of 56 months; those who could not have an optimal surgery had median OS of 27 months
- Multivariate analysis showed a long disease-free interval prior to surgery and localized disease identified those patients likely to benefit from this approach

- Note that most data supporting secondary surgery has been obtained from single-institution retrospective studies; GOG aims to answer this question definitively in the context of GOG 213.[42] Women with platinum-sensitive relapse who are felt to be surgical candidates will be randomized to surgery or no surgery. A separate randomization will take place in the chemotherapeutic program in which women will receive carboplatin and paclitaxel, with or without bevacizumab.
- Chemotherapy remains the mainstay of treatment of platinum-sensitive disease and women in this category are candidates for retreatment with a platinum-based combination. This is currently the standard of care with data from clinical trials to help guide management.
- Multiple trials have been performed in this specific population with results summarized in Table 1-5.[43–47] Seminal trials of importance are reviewed in greater detail.
  - The International Collaboration for Ovarian Neoplasms (ICON) and the German Cooperative Group (AGO) performed a randomized trial of paclitaxel with platinum (cisplatin or carboplatin) treatment versus conventional platinum therapy (nontaxane) in the ICON4/AGO-OVAR-2.2 trial, which involved 802 patients.[44]

Table 1-5: Randomized Trials in Platinum-Sensitive Recurrent Disease

Study	Regimen	N	Response Rate (%)	PFS (mos)	OS (mos)
Gordon et al.[42]	PLD Topotecan	220	28 28	7.3 5.8	27 18
ICON-4[43]	Platinum vs. Platinum-paclitaxel	804	54 66	10 13	24 29
AGO[44]	Carboplatin vs. Carboplatin-gemcitabine	356	31 47	5.6 8.6	17.3 18
Bolis et al.[45]	Carboplatin vs. Carboplatin-epidoxorubicin	190	36 31	3y: 12% 25%	5y: 22% 29%
Pujade-Luraine et al.[46]	Carboplatin+PLD vs. Carboplatin+paclitaxel	219	NR	11.3 9.4	NR

PLD: pegylated liposomal doxorubicin; NR: not reported.

- PFS favored paclitaxel plus platinum (HR 0.76; 95% CI 0.66 to 0.89)
- Survival curves favored paclitaxel plus platinum with a nearly 20% reduction in the risk of death associated with treatment using paclitaxel (HR 0.82; 95% CI 0.69 to 0.97)

- The AGO also conducted a trial comparing the use of carboplatin and gemcitabine (CG) to carboplatin and paclitaxel (CP) in this population.[45]
  - Median PFS using CG was 8.6 months, which was longer than that noted for CP at 5.8 months (HR 0.72; 95% CI 0.58 to 0.90)
  - Overall response rate also favored CG over CP, 47% versus 31% ($p = 0.0016$)
- An international randomized trial involving 974 women with platinum-sensitive relapsed compared carboplatin when given with pegylated liposomal doxorubin (CD) or paclitaxel (CP)[47]
  - Total incidence of grade 3–4 neutropenia was 35% with CD versus 46% with CP ($p < 0.01$); however, that of grade 3–4 thrombocytopenia was increased with CD over CP (16% versus 6%, $p < 0.01$)
  - Incidence of significant neuropathy was significantly higher with CP compared to CD, 5% versus 28% ($p < 0.001$); this difference still evident 15 months following randomization
  - Less carboplatin hypersensitivity reactions seen with CD (2%) over CP (9%)
  - Median PFS favored CD over CP at 11.3 versus 9.4 months (HR 0.82; 95% CI 0.72 to 0.94)

Platinum-Resistant or Recurrent Ovarian Cancer

- Women who progress while on platinum-based treatment or else relapse within 6 months of completing therapy comprise a group with a poor prognosis, in which treatment is neither very successful nor curative.
- Goals of treatment should be directed at symptom palliation and disease control, both of which are reasonable and achievable.

Table 1-6: Single Agents with Activity in Platinum-Resistant Recurrent Ovarian Cancer

Agent	ORR %	Median PFS (mos)	Median OS (mos)
PLD[42]	16	2.3	9
Topotecan[42]	8	3.4	10.3
Gemcitabine[47]	23	10.6	6.7
Vinorelbine[48]	21	3.1	10.1
Etoposide[49]	26.8	5.7	10.8
Irinotecan[50]	17.2	2.8	10.1
Pemetrexed[51]	21	2.9	11.4
Docetaxel[52]	35	5	8
Ifosfamide[53]	12	NR	9

PLD: pegylated liposomal doxorubicin; ORR: overall response rate; PFS: progression-free survival; OS: overall survival; NR: not reported.

- Given the palliative nature of treatment in this setting, single-agent chemotherapy remains the standard of care. Table 1-6 lists those chemotherapeutic agents considered active in this disease.[43,48–54]

Combination Therapy Should Be Avoided

- Bolis et al. compared paclitaxel to paclitaxel and epidoxorubicin in a randomized phase III trial involving 81 patients.[55]
  - Overall response rate was 34% with the combination and 17% with single-agent paclitaxel (p = NS)
  - Did not translate to a survival advantage with 2-year OS of 18% with single-agent paclitaxel and 10% with the combination.

- Brewer et al. looked at the combination of cisplatin and gemcitabine in a phase II trial for the GOG.[56]
  - Overall response rate was 16% with median survival of 14.9+ months

Novel Agents

- Angiogenesis inhibitors among the agents being actively studied in ovarian cancer
- Of those in clinical trials, bevacizumab, a monoclonal antibody directed against the vascular endoethelial growth factor receptor type A (VEGFR-A), has the most data; summarized in Table 1-7[57–62]

Small Molecule Tyrosine Kinase Inhibitors

- AZD2171 is a novel oral tyrosine kinase inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2), VEGFR-1, and c-kit. Matulonis and colleagues reported the initial results of this agent in the management of patients with recurrent ovarian cancer.[63] An overall response rate of 18.5% was reported among 28 patients treated. Three of these patients had platinum-resistant disease.
- Pazopanib is an orally available angiogenesis inhibitor of VEGFR-1, -2, and -3, platelet-derived growth factor receptor (PDGFR) -α and -β, and c-kit. Friedlander et al. have reported activity with pazopanib in women with advanced epithelial ovarian cancer.[64] Eleven of 36 subjects (31%) experienced a CA-125 response to pazopanib, with a median time to CA-125 response of 29 days and median duration of response of 113 days. Excluding one subject whose CA-125 decreased before she received the first dose, the biochemical response was 28% (10 subjects). Overall response rate based on modified Gynecologic Cancer Intergroup (GCIG) criteria (incorporating CA-125, Response Evaluation Criteria in Solid Tumors [RECIST], and clinical assessment) was 18% in subjects with measurable disease at baseline, and was 21% in

Table 1-7: Early Trials of Bevacizumab in Ovarian Cancer

Study	N	Prior Lines	Combination with Chemotherapy?	Platinum Status	ORR (%)	PFS (mos)	OS (mos)
Burger[55]	62	1–2	No	S/R	21	4.7	17
Cannistra[56]	44	2–3	No	S/R	15.9	4.4	10.7
Garcia[57]	70	1–3	Yes	S/R	24	7.2	16.9
Chura[58]	15	5–15	Yes	S/R	43	3.9	NR
Nimeiri[59]	13	1–3	Yes	S/R	15	4.1	11
Monk[60]	32	2–10	No	R	16	5.5	6.9

S: platinum-sensitive; R: platinum-resistant.

subjects without measurable disease at baseline. The median PFS was 84 days.

Palliative Care

- Increasingly important part of a patient's care
- Involves a multidisciplinary approach from multiple services
  - Surgical
  - Medical oncology
  - Pain and palliative care
  - Interventional radiology
  - Nutrition
  - Psychiatry
  - Social work
- Surgery may play a role in the palliation of certain patients
  - Bowel obstruction
    - Chemotherapy very unlikely to reverse this, so may be a sentinel event indicating the terminal phase of the illness
  - G-tube for decompression
  - Catheter for ascites drainage
- Biological agents currently being explored for palliative care of patients with refractory ascites
  - Catumaxomab
    - The trifunctional antibody catumaxomab (anti-EpCAM x anti-CD3) enhances the antitumor activity by redirecting T-cells and Fc-gamma receptor I/III–positive accessory cells to the tumor. It was piloted in a phase I/II trial involving 23 women.[65] Drug-related side effects included transient fever (83%), nausea (61%), and vomiting (57%). However, treatment with catumaxomab resulted in significant and sustained reduction of ascites with 22 of the 23 not requiring paracentesis after the last treatment dose, extending up to the end of study at day 37.

CHAPTER 2

Borderline Malignancy of the Ovary

Epidemiology

- Represent a separate entity of ovarian tumors; approximately 13% of epithelial ovarian neoplasms[66]
- Vast majority diagnosed at an early stage
- Typically a diagnosis of younger women, with median age at presentation in the fourth decade

Classification

- Characterized by cellular proliferation and nuclear atypia but no stromal invasion
- Histological variants include:
  - Serous, which represent the majority of tumors; involve both ovaries 50% of the time
  - Mucinous
  - Endometroid
  - Clear cell
  - Mixed

Diagnosis

- Sonographically can be difficult to distinguish from invasive ovarian cancers
- CA-125 level may be elevated with low malignant potential (LMP) tumors, particularly in the presence of advanced disease
- Evidence of peritoneal spread may indicate the presence of either *invasive* or *noninvasive* implants: histologic finding of a noninvasive implant is indicated by the absence of disruption of the normal tissue planes; even with the presence of noninvasive implants, the risk of malignancy is less than 1%.[67]

Treatment

- Surgery is the cornerstone in the management of these neoplasms.
- Proper staging is defined as a meticulous exploration of the entire abdominal cavity as one would do for ovarian cancer.
- Fertility-sparing approaches have been used in the women interested in preserving reproductive options.[68]
- There is no proven benefit from adjuvant chemotherapy. Four trials from Norway revealed that adjuvant therapy did not improve survival.[69]
- Careful monitoring of patients is necessary because recurrences can occur with relapses documented many years out from the initial diagnosis.
- The risk of developing an invasive ovarian cancer remains low.

CHAPTER 3

Germ Cell Tumors

Epidemiology

- 20% to 30% of all ovarian tumors
- 95% benign cystic teratomas, also known as dermoid cysts
- For malignant ovarian disease: germ cell tumors 1% to 3% of cases
- Typically onset in childhood and young adulthood

Classification

- Tumors typically have associated tumor markers (listed in Table 3-1)
- Histologic types comprising this class listed in Table 3-2

Table 3-1: Tumor Markers Associated with Germ Cell Tumors

Germ Cell Tumor	Tumor Markers
Dysgerminoma	LDH hCG (less common)
Mixed germ cell tumor	hCG AFP
Choriocarcinoma	hCG
Endodermal sinus tumor	AFP
Embryonal carcinoma	AFP hCG
Immature teratoma	Usually none (AFP may be elevated)

Table 3-2: Classification of Non-Epithelial Ovarian Cancers: Germ Cell Tumors and Sex-Cord Stromal Tumors

Histological Type	Classification Schema	
Germ Cell	Dysgerminoma	
	Non-Dysgerminoma	Endodermal sinus tumor
		Embryonal carcinoma
		Teratoma
		Immature
		Mature
		Gonadoblastoma
		Mixed
Sex-Cord Stromal	Granulosa Cell Tumor	Adult Type
		Juvenile Type
	Androblastoma	Sertoli-Leydig
		Leydig
		Poorly differentiated (sarcomatoid)
	Thecoma-Fibroma	
	Fibroma	
Unclassified		

- Three categories based on World Health Organization (WHO) classification:
  - Benign tumors (dermoid cysts)
  - Malignant tumor arising from dermoid cysts
  - Primitive germ cell tumors of the ovary (These are female counterparts of testicular cancer and prognosis is dependent on histology of the malignant component. This portion will discuss these tumors specifically.)

- Dysgerminoma
  - 50% of malignant germ cell tumors
  - Occurs at all ages, but majority diagnosed under 30 years of age
  - Epidemiologically associated with pregnancy in some reports[70]
  - Marked by increased serum LDH; production of hCG may be seen
  - 85% of cases are unilateral
  - Tumor cells stain positive for placental-like alkaline phosphatase (PLAP) and vimentin
- Endodermal sinus tumor
  - 20% of malignant germ cell tumors; also known as yolk-sac tumors
  - Typically onset in children and women under 20 years
  - Clinical presentation as a rapidly growing abdominal mass with an associated alpha fetoprotein (AFP) rise
  - Rarely bilateral, but with evidence of spread to peritoneum or retroperitoneal nodes at diagnosis
  - Characteristic histologic feature is the Schiller-Duval body, a papillary structure lined by primitive columnar cells
  - Immunohistochemistry is positive for AFP, alpha-1 antitrypsin, and cytokeratin
- Embryonal carcinoma
  - Rare cancer, comprising 3% of ovarian malignant germ cell tumors
  - Typically presents in children and adolescents as an abdominal mass
  - Often have hormonal abnormalities such as precocious puberty, irregular uterine bleeding, amenorrhea, or hirsutism
  - Typically advanced at diagnosis; long-term survival has been reported[71]
- Choriocarcinoma
  - Rarely presents as a pure tumor; often part of a mixed germ cell cancer
  - Less than 1% of ovarian germ cell tumors
  - Typically occurs in children and young adults

- Immature teratoma
  - Composed of tissue derived from the three germ layers
  - Contains immature or embyronal strictures
  - Occurs most commonly in the first two decades of life
  - Rarely bilateral
- Other forms of germ cell tumors include:
  - Struma ovarii: composed of thyroid parenchyma, may exhibit clinical hyperthroidism
  - Carcinoid: uncommon, but can be associated with typical carcinoid syndrome

Diagnosis and staging

- Diagnosis should be suspected in a young woman presenting with an ovarian or abdominal mass.
- Supportive signs include elevated tumor markers, summarized in Table 3-1.

Treatment

- Adjuvant chemotherapy is recommended for ovarian germ cell tumors with the exception of (1) stage I pure dysgerminoma and (2) stage I, grade 1 immature teratoma.
- The combination of bleomycin 30 U/m^2 (capped at a dose of 30 units) weekly, etoposide 75 mg/m^2 on days 1–5, and cisplatin 20 mg/m^2 on days 1–5 (BEP) is the standard of care. Cycles are given every 3 weeks a total of 3 times.
  - Gershenson et al. treated 26 patients using BEP over a 6-year span at MD Anderson Cancer Center.[72] All underwent surgery and only four had disease after surgery. With BEP, all four had a complete response and 96% went in to remission. One death was reported that occurred 14 months after chemotherapy was started.
  - GOG 78 was a prospective single-arm study in which patients underwent surgical staging followed by three courses of BEP.[73] Ninety-one of 93 patients were in sustained remission with a follow-up range from 4 to 90 months.

- Follow-up of these patients is paramount, as indicated in the GOG experience; one patient developed an acute myelogenous leukemia 22 months after her diagnosis and a second developed a lymphoma over 5 years out from protocol treatment.

CHAPTER 4

Sex Cord Stromal Tumors

Epidemiology

- Account for approximately 5% of all ovarian cancers
- Peak incidence around perimenopausal age group
- Among the most hormonally active of the ovarian neoplasms; because of this, about 70% are diagnosed at an early stage

Classification

- Numerous types described (see Table 3-2); most common forms discussed further
- Granulosa cell tumors
  - Microscopically diagnosed by a stromal fibrosis surrounding tumor cords. The pathognomonic findings of these tumors are Call-Exner bodies, which appear as eosinophilic material surrounded by granulosa cells.
  - These tumors produce estrogen and women often present with excessive or dysfunctional vaginal bleeding.
  - Majority are diagnosed at stage I
  - Less than 8% are bilateral at diagnosis
  - Two types recognized:
    - Adult granulosa cell tumors:
      - Most common
      - Occurs in postmenopausal women with median in the fifth decade
      - Given hormonal stimulation, over 20% have an associated invasive uterine cancer; therefore hysterectomy recommended as part of surgery
      - Tumors may recur years after diagnosis

- Juvenile granulosa cell tumor
  - Occur more frequently in young adults with almost 80% occurring in women under 20[74]
  - Can result in sexual precocity
  - Tumors usually unilateral and given young age, propensity is for fertility-sparing approaches
  - Tumors marked by inhibin, a glycoprotein secreted by granulosa cells
  - Prognosis guided by stage; women with stage I or II disease have survival of 95% at 5 years, compared to 59% survival for women with stage III or IV disease[75]
- Sertoli-Leydig cell tumors
  - Rare tumors that originate from the gonadal stroma
  - Occur in all age groups but most common in young women
  - Clinical presentation with progressive masculinization due to excessive androgen production: hirsutism, temporal balding, deepening of the voice, and enlargement of the clitoris
  - Over 90% diagnosed at stage I
  - Prognosis dependent on stage and cellular differentiation[76]

Diagnosis

- Tumors associated with expression of inhibin
  - Hormone produced by granulosa cells within the normal ovarian follicle
  - Jobling et al. demonstrated that inhibin levels are correlated with disease status in 27 patients treated for granulosa cell tumors, showing that levels normalized with treatment but rose in the context of recurrent disease.[77]

Treatment

- Active regimens for these tumors given in Table 4-1[78,79]
- Combination of cisplatin, vinblastine, and bleomycin has been evaluated in European studies with good activity, including one trial conducted through the EORTC.[78]

Table 4-1: Chemotherapeutic Options for Sex-Cord Stromal Tumors

Regimen	Cycles	Duration	ORR (%)
Cisplatin 20 mg /m^2 IV D 1–5 Vinblastine 0.15 mg/kg D 1–2 Bleomycin 30 units/m^2 IV D 2; 15 mg D 15[76]	4	28 days	52
Bleomycin 20 units/m^2 IVP D 1 Etoposide 75 mg/m^2 IV D 1–5 Cisplatin 20 mg/m^2 IV D 1–5[77]	4	21 days	37

ORR: overall response rate; IVP: intravenous push.
*Dose capped at 30 units.

- Response rate was 52% among untreated and 77% in women previously treated with chemotherapy or radiation therapy in the adjuvant setting

- In the United States, the GOG evlauated BEP among women with advanced or metastatic tumors (n = 48).[79]
  - Bleomycin dosing was modified in the GOG trial to once every 3 weeks due to two deaths on trial when weekly dosing was attempted.
  - Protocol for sex cord stromal tumors calls for four cycles as opposed to the regimen in germ-cell tumors where three cycles is administered.
  - Overall response rate was 37%. PFS at 3 years was 69% in those chemotherapy naive and 51% in those previously treated.

CHAPTER 5

Malignant Mixed Mullerian Tumors of the Ovary (MMMT or Carcinosarcoma)

Epidemiology

- Comprise less than 1% of ovarian malignancies
- Median age at diagnosis is in the sixth decade
- Have agressive clinical behavior, despite agressive treatment
- Median survival less than 2 years from diagnosis[80]

Classification

- Tumors have two components: a malignant epithelial component (the carcinomatous element) and a malignant stromal component (the sarcomatoid component).
- Two types of MMMT defined by the sarcomatous component:
  - *Homologous MMMT* has elements with normal counterpart that is indigenous to normal ovarian tissue (i.e., leiomyosarcoma, fibrosarcoma)
  - *Heterologous MMMT* has elements not normally found in the ovary (i.e, rrhabdomyosarcoma, chondrosarcoma)

Treatment

- Few studies have addressed treatment specific to MMMT.
- Surgery remains the mainstay of treatment and tumor cytoreduction is the first step in management. However, single institution data suggest that up to half of women undergoing surgery will be left with residual disease.[81,82]
- Platinum-based therapy remains the standard option for adjuvant treatment though no prospective randomized trials have been performed; the response rates are high,

ranging from 80% to 100% with median survivals between 16 and 27 months.[83]

- The GOG evaluated ifosfamide with MESNA as a second-line treatment following platinum-based therapy.[84] The response rate was 18% among 28 patients with evaluable disease.

SECTION 2

Cancers of the Uterine Corpus

CHAPTER 6

Anatomy

- Uterus comprised of the corpus (uterine body), which terminates at the cervix
- Comprised of two layers: the endometrium and the myometrium
- Endometrium thickens in response to estrogen; in absence of pregnancy, is shed in response to progesterone, constituting the menstrual cycle
- Adenocarcinomas of the uterus begin in the endometrium; progression occurs through the myometrium and distally through the cervix
- Uterine sarcomas begin in the myometrium; comprise approximately 5% of all uterine tumors
- Rarely, uterine tumor arises from placental tissue, during or following an abnormal pregnancy; collectively called gestational trophoblastic neoplasia
- All of these tumor types will be discussed under separate sections.

CHAPTER 7

Adenocarcinoma of the Uterus

Epidemiology

- In the United States more than 40,000 women are diagnosed with endometrial cancer each year; over 7,000 women will die of their disease.[1]
- Fourth most common cancer in women; eighth most common cause of cancer death in women
- Most common presentation as abnormal uterine bleeding; thus most cases diagnosed at early stages with 70% patients diagnosed when disease is confined to the uterus. In such cases, the prognosis is generally good, with 5-year survival of 90% to 95% without additional treatment required beyond surgery.
- Two types described in the literature, described as Type I and Type II adenocarcinomas (Table 7-1).[85,86] They reflect differences in estrogen stimulation, genetic mutations, demographics, and natural history. The prognosis between them is also quite different, with type II adenocarcinomas being more aggressive and conferring a worse prognosis.

Risk Factors

- Type I adenocarcinomas are associated with states related to excess estrogen stimulation:
  - Obesity
  - Polycystic ovarian syndrome
  - Diabetes mellitus

  - Unopposed estrogen replacement with drugs such as tamoxifen or estrogen-only hormone replacement therapy
  - Hereditary nonpolyposis colorectal cancer syndrome
- Type II adenocarcinomas have no generally accepted risk factors associated with its diagnosis.

Table 7-1: Type 1 vs. Type 2 Endometrial Adenocarcinomas[84,65]

Parameter	Type I	Type 2
Age	50–60s	60–70s
Obesity	Common	Uncommon
Estrogen-related	Yes	No
Underlying endometrial histology	Hyperplasia	Atrophy
Precursor Lesions	EIN	EGD, EIC
Transition to malignancy	Slow	Rapid
Predominant Histology	Endometrioid	Papillary serous/ mixed
Associated Genetic mutations	MSI, PTEN	p53
Familial predisposition	HNPCC	None
Depth of myometrial invasion at diagnosis	Superficial	Deep
Metastatic pattern	Nodal, extra-peritoneal	Nodal, peritoneal
Synchronous ovarian cancer?	Yes	No
Prognosis	Good	Poor

EIN: intraepithelial neoplasia; EGD: glandular dysplasia; EIC: intraepithelial carcinoma. MSI: microsatellite instablility; HNPCC: hereditary nonpolyposis colorectal cancer.

Histologic Types

- Adenocarcinomas represent 95% of histologies found in the uterus. Specific subtypes are:
  - Endometrioid (75% to 80%)
  - Papillary
  - Secretory
  - Ciliated cell
  - Adenocarcinoma with squamous differentiation
  - Serous or papillary serous (UPSC)
  - Mucinous
  - Clear cell
  - Squamous
  - Undifferentiated

Symptoms

- Most women present with abnormal bleeding, defined as heavier than usual or as new onset bleeding in the postmenopausal patient
- Watery, blood-tinged discharge another presenting symptom; in time becomes more bloody
- Other symptoms include:
  - Dyspareunia
  - Dysuria
  - Pelvic pain
  - Abdominal bloating
  - Constipation

Diagnosis

- Initial work-up of abnormal or dysfunctional bleeding must consist of endometrial sampling
- For women with postmenopausal bleeding, endometrial biopsy (EMB) and dilation and curettage (D&C) have similar accuracy
- Ultrasound (US):
  - Commonly used to work-up women presenting with abnormal vaginal bleeding

- Risk of type 1 endometrial cancer correlates with the measured thickness of the endometrial lining on transvaginal US: endometrial thickness of 5 mm or greater has a sensitivity of 96% and a specificity of 61% for the diagnosis of endometrial cancer.[87]
- If endometrial thickness is less than 4 mm, cancer generally ruled out; however, this may miss up to 4% of cancers, particularly type 2 cancers.[88] In one study, the endometrial echo measured less than 4 mm in 17% of patients.
- However, findings by US were also noted and may be important in this group, including the presence of intracavitary fluid or endometrial lesions, overall enlargement of the uterus, or other myometrial lesions.[89]

- Other modalities: Computerized tomography (CT) and magnetic resonance imaging (MRI) have been evaluated in the staging of endometrial carcinoma. Although both can be useful for the evaluation of extrauterine disease, these modalities are imperfect in the determination of myometrial invasion.
  - Kim et al. evaluated the comparative diagnostic accuracy of US, CT, and MRI in a panel of 26 patients with endometrial cancer.[90] The accuracy of these modalities was 69%, 61%, and 89%, respectively. This translated into a sensitivity of 50%, 40%, and 90% and specificity of 81%, 75%, and 88%, respectively.
- Positron-emitting tomography (PET):
  - Increased endometrial fluoro-deoxyglucose (FDG) uptake is seen in both physiologic and malignant conditions of the ovaries, cervix, and uterus.[91]
  - In a retrospective study that compared MRI to PET combined with CT (PET/CT) in 53 patients with a known uterine corpus cancer, PET/CT was equivalent to MRI in detecting primary uterine tumors and nodal disease.[92] However, PET/CT had a sensitivity of 100% and specificity of 94% in detecting disease outside of the uterus. This translated into a positive predictive value of 62.5% and negative predictive value of 100%.[92]

- No imaging studies replace operative staging in providing prognostic information.

Staging

- Surgical staging is critical for determining prognosis and treatment in endometrial cancer.
  - GOG 33 was a surgicopathologic study of 1,180 women with stage I–II disease.[93] This study established the following:
    - Grade 3 tumor or adenosquamous histology associated with risk of relapse even in absence of metastatic disease at diagnosis
    - Women with grossly positive pelvic node involvement, ovarian involvement, or tumor involving the outer third of the myometrium are at high risk of aortic node involvement
- Standard surgical approach includes total hysterectomy, bilateral salpingoopherectomy, pelvic and paraaortic lymph node dissection and peritoneal washings.[94]
- Uterine papillary serous carcinoma (UPSC) or clear cell at biopsy: Omentum and peritoneal evaluation is recommended because nearly 70% will have extrauterine disease.[95]
- Nodal staging includes dissection of lymphatic tissue from the obturator, internal, external iliac, common iliac and para-aortic lymph node basins. Anatomic lymph node dissection, with sampling of multiple anatomic regions, has been associated with improved survival.[96]
- Comprehensive staging is recommended in all cases of endometrial adenocarcinoma. Controversy, however, exists as to whether there is a need to stage patients with low-risk disease, such as grade 1 superficially invasive endometrioid tumor. Recent reports, however, suggest that 19% of these patients may be upgraded and 10% upstaged based on staging results.[97]
- Laparoscopy has been evaluated as an alternative to traditional open surgery for women with endometrial cancers. GOG LAP-2 compared these two surgical approaches and

enrolled over 2,600 women.[98] Preliminary results indicate that there were fewer complications and shorter hospital stays associated with laparoscopy. Long-term survival data, however, are not yet available.

- Robotic-assisted surgery represents another alternative for minimally invasive surgery for endometrial cancer. Compared to traditional laparoscopy, it offers improved motion scaling and tremor filtration, which are both optimally utilized surgically.[99] Although randomized data is currently lacking comparing it to either laparoscopy or laparotomy, single-institution data is encouraging. In one experience from the University of Oklahoma, Seamon and colleagues showed that robotics was associated with a decreased need to convert to an open procedure compared to laparoscopy (12% versus 26%, respectively, $p = 0.017$) and with a reduction in overall operating time (305 versus 336 minutes, $p = 0.001$).[99]
- Staging of endometrial cancer is based on surgical findings using the FIGO Staging System. In 2009, the Staging System was revised and both the 1988 and 2010 systems are given in Table 7-2, parts (a) and (b).[5,6] Major changes in the new staging system include:
  - Staging requires inclusion of tumor grade.
  - Tumor limited to the endometrium with invasion to less than 50% of the myometrium is now considered stage IA disease.
  - Endocervical gland extension is no longer considered stage II disease, but is considered stage I disease.
  - Upgrading of stage based on positive peritoneal cytology is no longer done.
  - Nodal involvement is separated; IIIC1 constitutes positive pelvic nodes while IIIC2 refers to para-aortic node involvement with or without pelvic nodes being positive.

Table 7-2(a): 1988 FIGO Staging System for Endometrial Cancer[5]

Stage	Characteristics
I	Tumor limited to the uterine corpus
IA	Tumor limited to endometrium
IB	Invasion to less than 50% of the myometrium
IC	Invasion to greater than 50% of the myometrium
II	Tumor involves the corpus and cervix only
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
III	Tumor extends outside the uterus but is confined to the true pelvis
IIIA	Tumor invades serosa and/or adnexa and/or positive peritoneal cytology
IIIB	Vaginal metastases
IIIC	Pelvic and/or para-aortic node involvement
IV	Involves bladder or bowel mucosa or distant spread identified
IVA	Invasion of the bladder or bowel mucosa
IVB	Distant metastases, including intra-abdominal and/or inguinal node involvement

Table 7-2(b): 2009 FIGO Staging System for Endometrial Cancer. All Stages Include Grade of Tumor. Changes are Highlighted in Bold.

Uterine Cancer Staging

Stage	Characteristics
I	Tumor limited to the uterine corpus
IA	**No or less than** 50% of the myometrium
IB	Invasion **equal or** greater than 50% of the myometrium
II	Tumor **invades cervical stroma but does not extend beyond the uterus**
III	Local and/or regional spread of the tumor
IIIA	Tumor invades serosa of the uterine corpus and/or adnexae
IIIB	Vaginal and/or parametrial invasion
IIIC	Metastases to the pelvic and/or paraaortic node involvement
	IIIC1 Positive pelvic nodes
	IIIC2 Positive para-aortic nodes with or without positive pelvic nodes.
IV	Involves bladder or bowel mucosa or distant spread identified
IVA	Invasion of the bladder or bowel mucosa
IVB	Distant metastases, including intra-abdominal and/or inguinal node involvement

- The primary staging criteria is as follows:
  - Stage I: cancer is limited to the uterine corpus
  - Stage II: cancer has spread from the corpus and involved the cervix

- Stage III: spread of cancer outside of the uterus but confined to the pelvis
- Stage IV: cancer has spread to bladder or rectum or evidence for metastatic disease

Treatment

Adjuvant Therapy

- Decisions are guided by stage and presence of high-risk factors.
  - Goals of adjuvant treatment are to achieve local control and to reduce risk of relapse or metastases. With these goals in mind, considerations for adjuvant management include the use of radiation therapy and/or chemotherapy.

Radiation Therapy

- Multiple trials have evaluated the role of adjuvant radiotherapy:
  - Aalders et al. conducted a study in Norway evaluating 540 women with clinical stage I disease. Patients in this study had a TAH-BSO without nodal sampling or assessment of peritoneal cytology and all received vaginal brachytherapy (60 Gy) prior to randomization to pelvic radiation (40 Gy) or no further treatment.[100] Five-year survival between both arms was equivalent (89% versus 91%).
  - GOG 99 was a randomized trial of pelvic radiation or observation as a treatment following surgical therapy for stages IB–II endometrial cancer with intermediate risk (age >70 and any of the following: grade 2 or 3; distal third myometrial invasion; or lymphovascular space invasion. If age >50, must have two of three factors; any age included if all three factors present).[101] The use of pelvic radiation in this group was associated with a significant improvement in recurrence rates favoring the use of pelvic radiation (3% versus 12%, $p = 0.007$). However, 4-year OS was not significantly affected (92% with pelvic radiation versus 85%

with observation). In addition, severe GI toxicity was seen in 8% of patients (3-year crude rate) receiving pelvic radiation with two patients dying from intestinal injury and an additional six who went on to develop a severe small bowel obstruction.

- PORTEC (Postoperative Radiation Therapy in Endometrial Cancer) Trial was another trial that randomized 715 patients who underwent TAH-BSO to pelvic radiation or observation.[102] Patients were not required to undergo a lymph node assessment. At 8 years of follow-up, pelvic radiation was not associated with a survival advantage, but pelvic radiation was associated with a significant reduction in locoregional recurrence (4% with pelvic radiotherapy versus 15% without, $p < 0.001$). In this group who did not undergo comprehensive surgical staging, the rate of severe GI toxicity at 5 years was only 3%.
- Lee et al. reported the results of a retrospective study on the effect of adjuvant radiotherapy in women with early-stage endometrial cancer (stage IA–C, node-negative) utilizing data from the Surveillance, Epidemiology, and End Results (SEER) program of the U.S. National Cancer Institute.[103] This analysis, which included over 20,000 women, showed that adjuvant radiotherapy was associated with statistically significant benefits in both OS and cancer-specific survival, particularly in stage IC grade 3, stage II grade 2, and stage I–II.
- Grade 3–4 tumors: Additionally, Lee and colleagues observed similar survival advantages for women who underwent surgical node examination at the time of hysterectomy (HR 0.59; 95% CI 0.39, 0.90).

Combined Modality Therapy: Chemotherapy and Radiation

- Combined approaches utilizing both chemotherapy and radiotherapy have been evaluated, albeit not sufficiently:
  - GOG 34 was a randomized trial evaluating the use of doxorubicin versus no further treatment following

surgery and radiotherapy in 92 women with stage I–II disease with one or more of the following risk factors: more than 50% myometrial invasion, pelvic or aortic node involvement, cervical involvement, or adnexal metastases.[104] At 3 years, there was no statistically significant difference in PFS or OS seen. In addition, there was a 7% rate of significant small bowel obstruction following radiation therapy.

- The EORTC conducted trial 55991 (EORTC 55991) in 367 women with high-grade stage I–IIIC endometrial cancer, and it was terminated early due to slow enrollment.[105] This trial sought to compare radiation therapy to chemotherapy administered pre- or postradiation. Regimens were not standardized but all utilized an anthracycline and a taxane. Both PFS and OS favored this combined approach with PFS of 74% with radiation therapy alone versus 83% with combined treatment ($p = 0.01$) and OS of 78% versus 88%, respectively ($p = 0.02$).

Metastatic or Advanced Disease

Surgery

- Surgery for locally recurrent disease has also been looked at, albeit in single institution settings.
  - At Memorial Sloan-Kettering, Barakat et al. reported on 44 patients who underwent a pelvic exenteration for centrally recurrent disease.[106] In their experience, 20% achieved 5-year disease-free survival, although operative morbidity occurred in 80% including abscess or fistula formation, septicemia, and thromboembolic complications. Therefore, careful consideration must be used in identifying appropriate patients for this potentially curative approach.

Radiation Therapy

- Despite the commonly held belief that women who relapse in the vagina or pelvis (locally recurrent disease)

can be treated with radiation therapy at that time with excellent outcomes, published data suggest that their outcome is poor, even with radiotherapy.

- Lin et al. published results in 50 women treated with radiation therapy for local recurrence.[107] Ten-year disease free and OS was 55% and 40%, respectively. Significant predictors of OS were tumor grade (grade 3, $p = 0.002$), age ($p = 0.02$), and tumor size at recurrence ($p < 0.001$).

Endocrine Therapy

- The use of hormonal agents can be considered as a therapeutic option in women with relapsed endometrial cancer, although data suggests its use is limited to women with low-grade disease.
  - GOG 81 was a trial of medroxyprogesterone acetate (MPA) at a low dose (200 mg/day) versus a high dose (1,000 mg/day).[108] The overall response rate was 25% versus 15%, respectively. Median PFS was 3.5 and 2.5 months, respectively with median OS of 11 and 7 months, respectively. It also demonstrated that benefit would be seen particularly in grade 1 or progesterone-receptor positive tumors.

Chemotherapy: First-Line Treatment

- Chemotherapy for advanced disease has been evaluated in multiple trials where it was compared to radiation therapy. In all of these trials, a survival advantage was seen with the use of chemotherapy. The seminal trials are listed:
  - GOG 122 was a randomized trial of whole abdominal radiotherapy (WAR) versus the combination of doxorubicin and cisplatin.[109] It was open to women with stage III–IV disease who underwent surgical assessment and had a maximum of 2 cm disease postoperatively. With 60 months of follow-up, the use of chemotherapy was associated with a 20% reduction in the risk of progression and a 32% improvement in survival, compared to WAR. This trial also demonstrated a change in the

patterns of relapse depending on how women were treated. Those treated with chemotherapy had more relapses in the pelvis (11.3% versus 8.4%) and liver (7.2% versus 3.5%); those treated with WAR tended to occur more often in the peritoneal cavity (16.3% versus 11.3%) and outside of the abdomen (18.3% versus 9.8%).

- Japanese GOG trial 2033 randomized 385 women with stages IC–III endometrioid adenocarcinomas to whole-pelvic radiation therapy (WPRT) versus chemotherapy using the regimen cisplatin, doxorubicin, and paclitaxel (CAP).[110] PFS at 5 years was 83% versus 82%, respectively ($p = 0.01$). OS was 85% and 87%, respectively. In subgroup analysis, a high-risk group defined as (1) stage IC patients over the age of 70 with grade 3 endometroid tumors or (2) stage II or IIIA patients, chemotherapy was associated with improvement over WPRT in terms of both PFS (84% versus 66%, $p = 0.024$) and OS (90% versus 74%, $p = 0.006$).
- The Italian group also evaluated whole pelvic/abdominal radiation versus CAP in 367 women with stage I grade 3–IIIC tumors.[111] Similar results were seen in terms of both PFS (63% in both arms) and OS (69% versus 66%, respectively).
- GOG 184 is the most recently completed randomized trial in which 552 women with advanced disease underwent surgical debulking followed by volume-directed radiation therapy (depending on surgical findings) and randomization to doxorubicin and cisplatin (AP) ± paclitaxel (TAP).[112] Women receiving paclitaxel experienced more severe and frequent hematologic, neuropathic, and muscle-related toxicities. At 3 years, the proportion of patients alive and free from recurrence was similar (62% AP versus 64% TAP). The overall hazard for recurrence or death of TAP compared to AP was 0.90 (95% CI, 0.69–1.17). In women with gross residual disease at time of enrollment, however, TAP was associated with a 50% reduction in the risk of relapse or death (HR 0.50; 95% CI 0.26–0.92).

- GOG 209 is a recently completed trial that builds on this experience and aims to establish whether a less-toxic regimen is equivalent or superior to CDP.[113] Women with stage III or IV endometrial cancer were randomized to CDP versus carboplatin and paclitaxel. Adjuvant radiation therapy is allowed, provided it is performed prior to the start of treatment. The results of this study are eagerly anticipated.

- Treatment of the chemo-naive patient with metastatic or advanced disease is less of an issue today, given the more frequent use of adjuvant chemotherapy on the basis of previous trials. However, women with disease not considered to be at high risk may still recur. For these women, multiple phase II trials have been conducted evaluating chemotherapy as a first-line treatment (Table 7-3).[114–122]
  - Combination chemotherapy:
    - GOG 163: Doxorubicin and cisplatin (AP) versus doxorubicin and paclitaxel (AT).[123] This trial enrolled 157 women with measurable disease (advanced or recurrent). For treatment with AP versus AT, the overall response rate (ORR) was 40% versus 43%, respectively, which was not a significant difference. The rate of complete (CR) and partial remissions (PR) were 15% and 25% with AP, respectively, and 17% and 26% with AT.
    - GOG 177: AP with or without paclitaxel. In this trial, paclitaxel was administered as a 24-hour infusion.[124] A total of 273 patients participated in this study. The combination of paclitaxel with doxorubicin and cisplatin (TAP) was associated with an improved complete response rate (22% versus 7%), partial response rate (36% versus 27%), and an increase in median PFS (8.3 versus 5.3 months) and OS (15.3 versus 12.1 months) over AP. TAP was associated with increased neuropathy and GI toxicity, with five treatment-related deaths observed in the TAP arm, whereas no toxic deaths were noted with AP.

Table 7-3: First-line Phase II Chemotherapy Trials in Endometrial Adenocarcinoma

First Author	Agent	N	Response Rate (%) CR	PR	Overall	Stable Disease (%)
Thigpen[112]	Doxorubicin 60 mg/m^2 every 3 weeks	43	26	12	38	30
Slayton[113]	Etoposide 100 mg/m^2 D 1, 3, 5 every 4 weeks	29	0	3	3	45
Thigpen[114]	Hexamethtylmelamine 280 mg/m^2 daily D 1–14 every 3 weeks	34	5.9	2.9	8.8	47
Thigpen[115]	Cisplatin 50 mg/m^2 every 3 weeks	49	4	16	20	45
Muss[116]	Methotrexate 40 mg/m^2 every weeks	38	6	6	12	55
Broun[117]	Vincristine 1.4 mg/m^2 weekly $\times$ 4 then every other week	33	3	15	18	38
Sutton[118]	Ifosfamide 1.2 g/m^2 with mesna 300 mg/m^2 every 4h $\times$ 3 daily for 5 every 4 weeks	33	6	18	24	NR
Ball[119]	Paclitaxel 250 mg/m^2 every 3 weeks (over 24 hours)	28	14.3	21.4	36	36
Homesley[120]	Pegylated liposomal doxorubicin 40 mg/m^2 every 4 weeks	52	3.8	7.7	11.5	60

NR: not reported.

Second-Line Therapy

- For women who experience progression or recurrence following first-line chemotherapy, cytotoxic options are particularly limited.
  - Phase II trials have been performed in this setting, but few agents have been found to be sufficiently active (Table 7-4).[125–131]
  - Second-line therapy for endometrial adenocarcinoma remains an unmet medical need; there are no FDA-approved agents in this setting.
    - Active agents in this setting are few but include:
      - Paclitaxel, which showed an overall response rate of 27% in 44 women.[125] Doses administered ranged from 110–200 mg/m^2 over 3 hours, every 3 weeks. This response rate was noted in women who did not receive prior taxane therapy.
      - Ifosfamide 1.2 gm/m^2 daily for 5 days every 4 weeks showed a 15% response rate in 52 women.[126]
      - Oxaliplatin 130 mg/m^2 every 3 weeks was also active in 54 women, with a response rate of 13.5%.[128]
      - Ixabepilone 40 mg/m^2 given every 3 weeks showed a response rate of 12%.[131] This was notable as patients in this trial had received prior taxane-based therapy. In a similar population, docetaxel was not an active agent.[130]
- Biologic agents have also been evaluated in endometrial adenocarcinoma.
  - mTOR (mammalian target of rapamycin) inhibitors: mTOR is a downstream target of a very important signaling cascade, which also involves PI3-kinase (phosphotidylinositol-3 kinase) through the inactivation of PTEN (phosphatase with tensin homology), which itself is a common mutation in endometrial cancers. A phase II trial of the mTOR inhibitor temsirolimus in chemotherapy-naive recurrent or metastatic endometrial cancer showed encouraging results with five partial responses among 19 patients.[132] However,

Table 7-4: Second-line Phase II Chemotherapy Trials in Endometrial Adenocarcinoma

First Author	Agent	N	Response Rate (%)			Stable Disease (%)
			CR	PR	Overall	
Lincoln[123]	Paclitaxel 110–200 mg/m^2 every 3 weeks	44	6.8	20.5	27	NR
Sutton[124]	Ifosfamide 1.2 g/m^2 for 5 days every 4 weeks.	52	7.5	7.5	15	NR
Thigpen[125]	Cisplatin 50 mg/m^2 every 3 weeks	25	0	4	4	80
Fracasso[126]	Oxaliplatin 130 mg/m^2 every 3 weeks	54	5.8	7.7	13.5	29
Muggia[127]	Pegylated liposomal doxorubinc 50 mg/m^2 every 4 weeks	42	0	9.5	9.5	NR
Garcia[128]	Docetaxel 36 mg/m^2 weekly	27	0	7.7	7.7	30.8
Dizon[129]	Ixabepilone 50 mg/m^2 every 3 weeks	50	2	10	12	60

NR: not reported.

a subsequent study of the same agent in women previously treated with one prior chemotherapy regimen showed a dramatic reduction in activity with only two responses (7%) seen in 27 women.[133] Other agents of this class (everolimus, deferolimus) continue in clinical trials.

- Angiogenesis inhibitors are also of potential therapeutic value in this cancer. A phase II study of thalidomide was the first to demonstrate an association between elevated plasma levels of VEGF (vascular endothelial growth factor) and prognosis.[134]
- Aghajanian et al. presented a phase II study of bevacizumab in the treatment of recurrent endometrial cancer.[135] Fifty-two patients who had received up to two prior chemotherapy regimens for endometrial cancer were enrolled. The overall response rate was 13.4% with 40% experiencing PFS for at least 6 months. The median PFS was 4.2 months and median OS was 10.5 months.
- A study looking at the antiangiogenic agent aflibercept (VEGF-Trap) has completed accrual through the GOG and results are anticipated.[136]

CHAPTER 8

Stromal Tumors of the Uterus

Epidemiology

- Uterine sarcomas comprise less than 5% of all uterine malignancies
- Peak incidence in the fifth decade

Histopathology

- Pathologic criteria used to define malignant smooth-muscle tumors from benign entities: (1) coagulative tumor cell necrosis; (2) diffuse atypia (moderate to severe); and (3) more than 10 mitoses per high power field.
- Tumors with only one of these criteria and otherwise not meeting classification criteria for malignancy are commonly referred to as smooth-muscle tumors of unknown malignant potential (STUMP).
- Classification dependent on pathologic resemblance to mesenchymal tissue:
  - Endometrial stromal sarcoma (ESS)
    - 10% of all uterine sarcomas
    - Considered low-grade neoplasms
    - Can be confused with proliferative endometrium if seen on curretage
    - Requires hysterectomy for definitive diagnosis because the interface between endometrium and myometrium must be evaluated
  - Undifferentiated sarcomas
    - Endometrial stromal sarcomas in appearance, but differ by their greater degree of anaplasia and lack of branching vasculature seen in ESS
  - Leiomyosarcoma
    - 1% to 2% of all uterine malignancies; 30% of all uterine sarcomas

- 40% to 80% of tumors may be hormone receptor positive. In some studies, this has been shown to be a prognostic indicator in women with this disease.[137]

- MMMT or carcinosarcoma
  - Classified as dual population of malignant cells with one arising from an epithelial component (carcinoma) and one arising from mesenchymal component (sarcoma)
  - Mesenchymal component can differentiate into tissue not normally found in the uterus such as skeletal muscle (rhabdomyosarcoma) or cartilage (chondrosarcoma); presence of these extrauterine patterns of differentiation referred to as heterologous tumors
- Mullerian adenosarcoma
  - Typically low-grade malignancy characterized by benign glandular elements (adenoma) coupled with the malignant mesenchymal proliferation (sarcoma)
  - High-risk variants generally identified by the presence of high mitotic index and sarcomatous overgrowth[138]

Symptoms

- Symptoms are nonspecific.
- Pelvic symptoms such as vaginal bleeding, vaginal discharge, or urinary symptoms may predominate.
- Abdominal distention or shortness of breath may be signs of advanced disease.
- Pulmonary metastases seen in metastatic disease.

Diagnosis and Staging

- Zivanovic et al. evaluated the utility of staging of leiomyosarcoma using FIGO versus the American Joint Comission on Cancer (AJCC) staging for endometrial adenocarcinoma.[139] AJCC staging upstaged patients when compared to FIGO. Comparing between them, markedly

different age-specific survival outcomes were seen. They concluded that neither system ideally stratified patients by stage and suggested that perhaps a specific system to stage these patients be formulated.

- FIGO revised uterine cancer staging in 2009 to provide for a separate classification for uterine sarcomas, and the AJCC has adopted these changes.[6] The AJCC classification is given in Table 8-1.

Table 8-1: Uterine Sarcoma Staging. All Stages Include Grade of Tumor. Changes are Highlighted in Bold.

Stage	Characteristics
I	Tumor limited to the uterine corpus
IA	Tumor 5 cm or less in greatest dimension
IB	Tumor more than 5 cm
II	Tumor extends beyond the uterus, but is within the pelvis
III	Local and/or regional spread of the tumor
IIIA	Tumor invades serosa of the uterine corpus and/or adnexae
IIIB	Vaginal and/or parametrial invasion
IIIC	Metastases to the pelvic and/or para-aortic node involvement
IIIC1	**Positive pelvic nodes**
IIIC2	**Positive para-aortic nodes with or without positive pelvic nodes**
IV	Involves bladder or bowel mucosa or distant spread identified
IVA	Invasion of the bladder or bowel mucosa
IVB	Distant metastases, including intra-abdominal and/or inguinal node involvement

Surgical Treatment

- Primary treatment involves hysterectomy and bilateral salpingo-oophorectomy (BSO).
- For clinically apparent stage I or II uterine sarcoma, yield of node sampling is low with less than 5% of patients having evidence of nodal involvement.[140]
- In presence of advanced disease, rate of node positivity increases substantially with Goff et al. noting a rate of 44% nodal involvement.[141]
- Presence of intraabdominal disease generally treated with debulking but intent is mostly palliative.[142]

Adjuvant Therapy Considerations

- Despite aggressive surgery, 50% of women with leiomyosarcoma are at risk of relapse within 2 years.[140]
- Adjuvant pelvic radiation is likely ineffective. Hornback et al. reported on the use of pelvic radiation in women with uterine sarcomas.[143] Compared to women who did not receive radiotherapy, there was no difference in PFS or 2-year survival in women with either leiomyosarcoma or mixed mesodermal tumors.
- Historically, chemotherapy has not been proven any more effective in the adjuvant setting, unfortunately. The GOG conducted a randomized trial of doxorubicin versus observation in women with early-stage fully resected uterine sarcomas; there was no difference in relapse rates or progression free or OS.[144] Specific types of sarcoma did not differ in terms of their recurrence rates, though leiomyosarcomas were noted to recur more commonly in the lungs while mixed mesodermal sarcomas appeared to relapse more often outside of the lungs.
- For uterine carcinosarcoma, a phase III trial of whole abdominal radiation versus ifosfamide and cisplatin was completed, enrolling 232 women with stage I–IV resected disease.[145] After adjustment for stage and age, the recurrence rate was 20% lower with the use of chemotherapy (HR 0.79; 95% CI 0.53, 1.176). Mortality was 29% lower with chemotherapy as well (HR 0.71; 95% CI 0.48–1.05).

Although not statistically significant, the differences were felt to be clinically meaningful and the GOG has since adopted this combination as standard of care.

- Adjuvant gemcitabine and docetaxel has also been evaluated specifically in women with high-grade uterine leiomyosarcoma.[146] Gemcitabine 900 mg/m^2 was given over 90 minutes on days 1 and 8 with docetaxel 75 mg/m^2 on day 8, every 21 days. Of 23 evaluable patients with stage III–IV disease at diagnosis, 45% are progression free at 2 years with a median PFS of 13 months. For 18 patients treated for stages I–II disease, almost 60% were progression free at 2 years with a median PFS of 39 months. OS had not been reached for either subset at the time of this report. These results require confirmation in a randomized trial, but remain very encouraging.

Treatment of Advanced or Metastatic Disease

- For women with advanced disease, multiagent chemotherapy is typically standard of care.
- A phase II study from the GOG evaluated carboplatin and paclitaxel as treatment in advanced, refractory, or recurrent uterine carcinosarcoma (MMMT).[147] Fifty-five patients participated in this study and 46 were evaluable for efficacy. The ORR was 52% (95% CI 37% to 67%); of these, 11% were complete responses. Given the promising activity, a phase III trial is anticipated that will compare this to the current standard of care (ifosfamide and cisplatin).
- Hannigan et al. reported the results of a trial of 74 patients with recurrent uterine sarcoma, receiving the combination of vincristine, actinomycin D, and cyclophosphamide.[148] The ORR was 28%, including a complete response rate of 13%. For complete responders, the median duration of response was 16 months; for those with a partial response, the median duration was 5 months. Overall 5-year survival was 15%.
- The GOG conducted a trial of doxorubicin given with or without DTIC (dimethyl-triazeno-imidazole-carboxamide) in women with stage III or IV recurrent uterine sarcomas.[149]

The response rates were 16% versus 24% favoring the combination ($p > 0.05$). Women with leiomyosarcomas survived longer than other cell types in this study (12 versus 6 months, $p < 0.001$) but a treatment effect was not observed. Despite this activity, the combination was also associated with far greater hematologic and/or gastrointestinal side effects. Hence, it is not a widely used regimen.

- The combination of docetaxel and gemcitabine has also been evaluated as a first-line or a second-line therapy after doxorubicin.[150,151] Hensley et al. reported the results of a phase II trial conducted at Memorial Sloan-Kettering in this population. As a first-line treatment, the combination was associated with a 36% ORR that included a 5% rate of complete responses. The median PFS was 4.4 months and median OS was 16+ months.[151] As a second-line therapy, the ORR was 27% with a 6.3% rate of complete responses. Stable disease was noted in 50% and median PFS was 5.6+ months.[150] While one could question the contribution of docetaxel to gemcitabine, it should be noted that a randomized phase II trial through the Sarcoma Alliance for Research did compare gemcitabine to the combination with docetaxel and showed that the combination of gemcitabine and docetaxel was associated with an improved response rate (16% versus 8%), longer PFS (6.2 versus 3 months), and longer OS (18 versus 12 months).[152]

CHAPTER 9

Gestational Trophoblastic Neoplasia (GTN)

Definition

- Applies to rare group of diseases with commonality being that tumor cells arise in the fetal chorion (which would normally become the placenta) during pregnancy
- Consists of specific histologic types, all of which carry differing prognoses:
  - Hydatidiform moles
    - Partial
    - Complete
    - Persistent
  - Gestational choriocarcinoma
  - Placental-site trophoblastic tumors
- Majority characterized by production of human chorionic gonadotropin (hCG)

Placental Anatomy and Evolution of GTN

- Placenta, formed following fertilization of a woman's egg, is comprised of three cell types: chorionic villi, cytotrophoblasts, and syncitiotrophoblasts. The villi contain fetal blood vessels and insert into the uterine lining. Cyto- and syncitiotrophoblasts provide a supporting role to the villi, enabling them to interface with maternal blood supply. hCG is a product of trophoblast cells.
- In GTN, the fetus generally does not develop, but growth of villi and the cytotrophoblasts and syncitotrophoblasts continues.

Epidemiology[153]

- Overall, they account for less than 1% of women's cancers of the reproductive tract.

- Within the United States and Europe, the incidence of molar pregnancies is reported to be about 1 in 1,500 to 2,000 pregnancies. The incidence in Asia is far higher, reported to be 1 in 120.
- Invasive moles affect 1 in 15,000 pregnancies.
- Choriocarcinoma affect 1 in 40,000 pregnancies within the United States, but it is more common in Asia.
- Twin pregnancies defined as a molar pregnancy occurring with a coexisting fetus have been reported, with an incidence of 1 in 22,000 to 100,000 pregnancies.

Risk Factors

- A number of risk factors have been described.[154–156]
- This is a disease of women of child-bearing age. For complete moles, women over 40 or under 20 appear to be at greatest risk.
- Women with a prior history of molar pregnancy are at risk for another one, with a quoted overall risk for a subsequent one at 1% to 2%. The risk increases if more than one molar pregnancy developed.
- Women who have had prior miscarriages or difficulty attaining pregnancy appear to be at increased risk.
- Women who have an A or AB blood type appear to be at slightly higher risk.
- Nutritional deficiencies in vitamin A and/or carotene intake has tracked with areas of higher incidence of molar pregnancy, though a case-control study from Berkowitz et al. did not support this association.[157,158]

Genetics and Pathology

- Partial moles arise when two sperm fertilize a normal egg, resulting in a triploid karyotype.
  - Microscopically, appears like grape-like villa, which can have evidence of a malformed fetus.
  - Trophoblast hyperplasia tends to be mild and focal.
- Complete moles are genetically characterized by paternal chromosomes without maternal contribution. While it is XX, this arises when one to two sperm fertilize an empty

egg. Despite this, the presence of maternal mitochondrial DNA within complete moles has been reported.[159]
  - Microscopically characterized by hydropic villi with trophoblast proliferation
  - Grossly, resembles large vesicles (classically referred to as a "bunch of grapes")
- Invasive moles demonstrate molar villi with evidence of myometrial or vascular invasion.
- Choriocarcinoma defines malignant transformation of a molar pregnancy, though it can spontaneously arise from the placenta.
  - Typically seen as a circumscribed hemorrhagic mass
  - Microscopically characterized as a dimorphic population of cytotrophoblasts and syncitiotrophoblasts
- Placental-site trophoblast tumors (PSTT) arise as a uterine mass.
  - Microscopically characterized as trophoblastic proliferation with evidence of infiltration; syncitiotrophoblasts rarely involved

Symptoms

- Complete molar pregnancies
  - Women with complete moles will commonly present with vaginal bleeding.
  - Over half may have uterine enlargement on examination.[160]
  - Signs and symptoms related to excessive hCG production may be present due to levels in excess of 100,000 mIU/mL. These include: hyperthyroidism, hypereme+sis gravidarum, and ovarian theca-luteal cysts greater than 6 cm.[160]
- Partial molar pregnancies
  - Women often will present with vaginal bleeding during pregnancy with concerns clinically of spontaneous or threatened abortion.
  - Symptoms associated with excess hCG tend not to occur in this group of women. For example, uterine enlargement was reported in 8% to 11% in two separate studies.[161,162]

- Invasive moles, choriocarcinoma, and PSTT
  - Symptoms are relatively nonspecific but may include signs of systemic illness including infection, abdominal pain or swelling, or a vaginal mass.
  - Shortness of breath or chest pain may indicate the spread of disease to the lungs, the most commonly affected site.
  - Seizures, headache, or paralysis is associated with spread of disease into the brain.

Diagnosis

- Higher than expected hCG levels generally raise the suspicion for a molar pregnancy. However, patients with PSTT typically have a low or normal hCG.
- Phantom hCG syndrome occurs when a woman has persistent but mild elevation of hCG, usually due to the presence of interfering heterophil antibodies, which can bind to other species' immunoglobulins, which are used in commercial kits for hCG measurement. Too often, it leads to overtreatment with chemotherapy for a presumed diagnosis of choriocarcinoma (hence, it is also referred to as pseudohypergonadotropinemia).[163] If concern is raised, serum hCG should be sent to a national reference laboratory for confirmation. Clinical clues that phantom hCG is present include (1) lack of hCG in the urine and (2) lack of decrease in hCG levels with serum dilution.
- Ultrasound is useful; a "snowstorm" pattern associated with the absence of a uterus in a woman thought to be pregnant is consistent with a molar pregnancy.
  - Characteristic findings by ultrasound of partial mole include (1) focal cystic changes, irregular appearance, or increased echogenicity in the placenta and (2) a ratio greater than 1.5 of the transverse versus anteropoterior dimension of the gestational sac. Fine et al. reported that in the presence of both criteria, the frequency of detection was 87%. When neither were present, the frequency of missed abortion was 90%.[164]
- Ultimately the diagnosis of GTN is based on histologic examination. Typically, it begins with analysis of

endometrial tissue obtained at D&C or, in the case of the pregnant patient, at dilation and evacuation (D&E). Given the absence of other symptoms prior to bleeding, the patient with partial mole may not have the diagnosis suspected prior to D&E. Biopsy of potentially metastatic sites is not recommended however as these tumors are highly vascular and may be prone to hemorrhage.

Staging

- The patient suspected of a molar pregnancy requires a comprehensive evaluation including quantitative hCG, chest X-ray (due to the frequent involvement of the lungs as the first site of metastatic disease), coagulation studies, liver and renal function tests, and thyroid function tests.
- Other studies may be determined based on the patient's risk of having or developing invasive GTN. It is noted that women with partial moles are in general at low risk of developing invasive disease, so risk stratification is generally applied to women with complete moles. For these women, high-risk features include hCG levels >100,000 mIU/mL, excessive uterine size, and prominent ovarian theca-lutein cysts.[160] In women with high-risk features, the incidence of metastatic disease was 8%, compared to 0.6% in women whose disease was considered to be at low risk.
- GTN is currently staged by a combined FIGO/WHO staging system that incorporates both the anatomic location of disease and risk factors into a common system (Table 9-1, parts (a) and (b)).[165] The staging/scoring system requires several criteria.
- GTN is diagnosed following D&E of a molar pregnancy if:
  - hCG plateau is documented over four or more values over at least 3 weeks.
  - There is a rise of 10% or more in hCG over at least 2 weeks.
  - There is a histologic diagnosis of choriocarcinoma.
  - Abnormal hCG levels persist 6 months or more after evacuation.

Table 9-1: FIGO Staging/Scoring System for Gestational Trophoblastic Neoplasia[163]

(a) FIGO Staging System

Stage I	Disease confined to the uterus
Stage II	Disease is outside the uterus but limited to the genital tract
Stage III	Disease involves the lungs
Stage IV	Other distant metastatic involvement

(b) Scoring System

FIGO Score	0	1	2	4
Age	≤39	>39		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	
Interval since index pregnancy (months)	<4	4–6	7–12	>12
Pre-treatment hCG (mIU/mL)	$<10^3$	10^3–10^4	$>10^4$–10^5	10^6
Largest tumor size (cm, includes uterus)	3–4	5		
Site of metastases		Spleen, Kidney	Gastrointestinal tract	Brain
Number of metastatic sites	0	1–4	4–8	>8
Prior failed chemotherapy			Single agent	Two or more agents

Low risk if score ≤6; High risk if ≥7.

- Metastatic evaluation must consist of:
  - Chest X-ray (considered adequate)
  - CT scan of the abdomen and pelvis
  - Radiologic examination for brain metastases; CT is acceptable, but MRI is preferred
- Patients who relapse or progress require restaging

Treatment

- For the woman presenting with a molar pregnancy, treatment begins with D&E. Following this, hCG levels are monitored to facilitate the diagnosis of persistent GTN. In this scenario, hCG levels should be followed weekly until levels are undetectable for at least a 3-week period.[166] Following this, levels should be followed monthly for 6 months and during this time, patients should be counseled to avoid subsequent pregnancy.
- For patients with persistent GTN, therapy is guided by both stage and risk score.
  - For low-risk, stage I disease, management is based on the patient's interest in fertility preservation.
    - If the patient is not interested in future fertility, the option of hysterectomy is reasonable. Although it can prevent the development of local invasive disease, it will not eliminate the risk of metastasis.[166] Hence, follow-up by serial hCG levels is still required.
    - Otherwise, fertility preservation mandates the use of single-agent chemotherapy and both methotrexate and actinomycin D are acceptable agents as initial treatment of low-risk GTN. Osborne et al. reported the results of a phase III trial conducted by the GOG in this population.[167] Two hundred-fifteen women with low-risk disease (FIGO score 0–6) were randomized to methotrexate 30 mg/m^2 weekly versus biweekly actinomycin D 1.25 mg/m^2 until normalization of their β-hCG levels for a minimum of 4 weeks. The complete response rate was 53% with methotrexate and 69% on actinomycin D ($p = 0.015$). However, toxicity was greater among

women treated with actinomycin D, as it causes more nausea, vomiting, and alopecia compared to methotrexate. Grade 4 neutropenia was also observed with those treated with actinomycin, but not with methotrexate.

- For stage II–III disease, the risk factor is used to determine treatment options.
  - Women with risk scores below 7 are deemed at low risk and can be treated with single-agent chemotherapy. hCG levels are followed to normalization but if plateau or rise occurs, which may herald drug-resistance, an alternative single agent is attempted, unless reevaluation shows the risk score has increased. In the latter case, multiagent therapy is recommended.
- For women with high-risk disease (7 or greater), intensive chemotherapy using multiple agents is recommended.
- Women with stage IV disease are at high risk for treatment failure. Therefore, multiagent therapy is advised.
  - EMA-CO is considered the standard of care for women with stage II–III high-risk or stage IV disease. The schedule of this combination is given in Table 9-2.
    - In the presence of brain metastases, a higher dose of methotrexate is utilized. Patients must be monitored closely because treatment may lead to CNS bleeding as tumor responds. **This is a neurosurgical emergency and requires prompt surgical treatment.**
    - Bower et al. reported on 272 patients with high-risk GTN treated at Charing Cross Hospital demonstrating that EMA-CO resulted in a 78% complete response rate.[168] High-risk features associated with a poor prognosis in this experience included presence of liver metastases, brain metastases, interval from the antecedent pregnancy, and a term delivery of that pregnancy. More importantly, young women had resumption of menses within 6 months of completing treatment, though age at menopause was notably younger (47 years) as compared to women who did not receive chemotherapy for a diagnosis of molar pregnancy (52 years).

Table 9-2: EMA-CO for High-Risk GTN[166]

Week One	EMA
Actinomycin-D	0.5 mg IVP × 2 days
Etoposide	100 mg/m² IVPB × 2 days
Methotrexate	300 mg/m² IVCI over 12 hours* *in presence of brain metastases, dose is increased to 1000 mg/m² IVCI over 48 hours.
Leucovorin	15 mg PO/IM every 12 hours for 48 hours. Start 24 hours after Methotrexate completed.* *when higher dose of Methotrexate is used, Leucovorin 15 mg is given every 6 hours for 48 hours with first dose starting 8 hours after Methotrexate is begun.
Week Two	**CO**
Vincristine	0.8 mg/m² IVP (Cap dose at 2 mg)
Cyclophosphamide	600 mg/m² IVPB

- For patients with PSTT or those who do not respond or progress on EMA-CO, standard second-line therapy consists of EMA-EP (Table 9-3). In another report from Charing Cross Hospital, 21 of 22 (95%) patients treated with EMA-EP after a plateau hCG on EMA-CO achieved remission.[169] Additionally, of 12 resistant to EMA-CO, 9 (75%) achieved a remission. Newlands also reported on eight patients treated with EMA-EP as primary therapy for PSTT and showed a 50% complete response rate. For women with PSTT who do not respond to chemotherapy, however, primary hysterectomy is recommended.
  - These regimens will expose patients to a significant amount of alkylating agents, which raises concern of secondary cancers. Rustin et al. reported that of almost 1,400 women in follow-up for GTN, 39 second cancers were diagnosed, which was higher than expected.[170] The incidence ratio was

Table 9-3: EMA-EP[167]

Week One	**EP**
Etoposide	150 mg/m^2 IVPB
Cisplatin	75 mg/m^2 IVPB
Week Two	**EMA**
Actinomycin-D	0.5 mg IVP
Etoposide	100 mg/m^2 IVPB
Methotrexate	300 mg/m^2 IVCI over 12 hours* *in presence of brain metastases, dose is increased to 1000 mg/m^2 IVCI over 48 hours.
Leucovorin	15 mg PO/IM every 12 hours for 48 hours. Start 24 hours after Methotrexate completed.* *when higher dose of Methotrexate is used, Leucovorin 15 mg is given every 6 hours for 48 hours with first dose starting 8 hours after Methotrexate is begun.

1.51 ($p = 0.001$) indicating that the use of combination chemotherapy increased the risk of secondary cancer by 50%. For secondary cancer, the risks were increased for developing leukemia (RR = 16.6; 95% CI 5.4–38.9); at 5 to 9 years, colon cancer (RR = 4.6; 95% CI 1.2–16.9); and breast cancer (RR = 5.8; 95% CI 1.2–16.9).

CHAPTER 10

Cervical Cancer

Anatomy

- Narrow cylindrical segment of the uterus that measures 2–4 cm and is contiguous with the inferior aspect of the uterine corpus, illustrated in Figure 10-1.

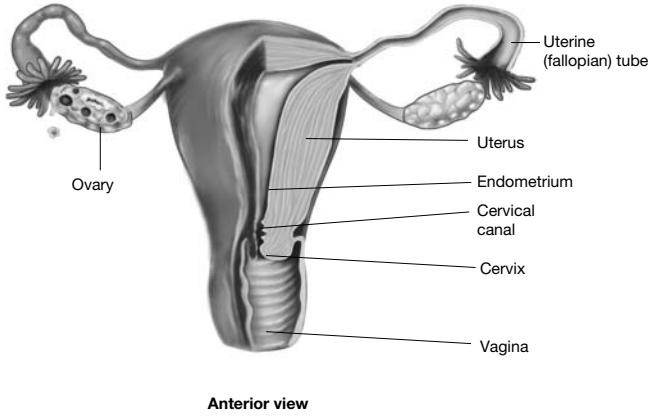

Figure 10-1: Female reproductive organs. Robert K. Clark, *Anatomy and Physiology: Understanding the Human Body*, Jones and Bartlett Publishers, copyright: 2005.

- The junction between the uterus and the cervix is termed the isthmus.
- Separated from the bladder by fatty tissue
- Connected laterally to the broad ligament and the parametrium
- Opens into the vaginal cavity through the external os
- Extends from the external os to the internal os where is joins the uterine cavity
- Histologically, the internal os is the site of transformation from endocervical to endometrial glands.

- The intravaginal part of the cervix (exocervix) is covered with stratified squamous epithelium.
- The endocervix mucosa is arranged in branching folds and is lined by cylindrical epithelium.

Epidemiology

- Incidence of cervical cancer has declined in the last six decades due to effective screening
- Least common gynecological malignancy in the United States
  - Each year, an estimated 11,070 new cases are reported with approximately 3,870 deaths.[171]
  - Peak age is 47 years of age.
  - Affects women from lower socioeconomic class, likely as a secondary result to lack of access to screening
  - Significant problem for women in developing countries and often represents the leading cause of death

Etiology and Risk Factors

- Risk factors for cervical cancer include:
  - Early onset of sexual activity
  - Multiple sexual partners
  - History of genital warts
  - Multiparity
  - Cigarette smoking
  - Oral contraceptives
  - Immunodeficiency states
  - Human papillomavirus (HPV):
    - Types 16 and 18 most commonly associated with cervical cancer and high grade dysplasias.
      - The viral DNA of these subtypes can be detected in at least 90% of all cervical cancers seen, particularly in the United States.
      - Two viral genes, E6 and E7, are invariably expressed in HPV-positive cervical cancer cells; their gene products are known to inactivate the major tumor suppressors, p53 and pRB, respectively.

Symptoms

- Intermenstrual bleeding
- Heavier menstrual flow
- Postcoital bleeding
- Bowel obstruction
- Renal failure
- Foul smelling vaginal discharge
- Pelvic pain
- Flank/Leg pain
  - Secondary to involvement of the ureters, pelvic wall, or sciatic nerves
- Rectal bleeding
- Obstipation
- Dysuria
- Hematuria
- Persistent edema of lower extremities
  - Secondary to lymphatic/venous blockade by pelvic side wall disease

Screening

- Fortunately, cervical cancer can be detected early via Pap smear.[172]
  - The Pap smear was introduced in 1943 and has resulted in a drop in the incidence of invasive cervical cancer by over 70%.[173]
  - Typically, it will detect cervical abnormalities and pre-invasive disease.
  - Today, Pap smears utilize liquid-based cytology, which has improved detection of suspicious lesions and has reduced unsatisfactory readings by cytopathologists by as much as 85%.[173]
  - Active screening has reduced the incidence of cervical cancer by as much as 90% within a 3-year period.[173]
- When to start screening
  - The American College of Obstetrics and Gynecology released new screening recommendations in 2009.[174] Cervical cancer screening should begin approximately

at 21 years of age, regardless of sexual history. Previously, screening was recommended to begin 3 years after the onset of sexual activity and no later than the age of 21. The change was made because the incidence of invasive cervical cancer is exceedingly low in this age group. In addition, there are risks associated with treatment, including an increased risk of premature birth in women undergoing excisional procedures for cervical dysplasia.

- Screening interval
  - Cervical screening should be performed every 2 years between the ages of 21 and 29. Review of the evidence suggests very little is to be gained through annual screening in this age group.
  - After the age of 30, women who have had 3 consecutive, technically satisfactory negative cytology results may be screened every 3 years.
  - More frequent screening may be used in those individuals who have a history of in utero DES exposure, are HIV positive, are immunocompromised, or have been previously treated for CIN2, CIN3, or cancer.
  - HPV DNA testing for primary cervical cancer screening is approved for women over 30 years of age. For this group, cervical screening may be performed every 3 years using conventional or liquid-based cytology combined with a test for DNA for high-risk HPV types, as an alternative to cervical cytology testing alone. However, this screening strategy should be made based on individualized discussions.
    - Women who test positive for HPV DNA should continue screening at the discretion of their healthcare provider.
  - Women who received HPV vaccination should continue cervical cancer screening.

- Screening for women posthysterectomy
  - Screening with vaginal cytology tests after total hysterectomy (with removal of the cervix) for benign gynecological disease is not indicated.
  - Women who have had a subtotal hysterectomy should continue cervical cancer screening.
  - Women with a prior history of high-grade intraepithelial lesions prior to hysterectomy or a history of CIN2 or CIN3 should continue to be screened.
  - Women with a history of in utero diethylstilbestrol (DES) exposure should continue screening after a hysterectomy.
- When to discontinue screening
  - At the age of 65 or 70 women who who have had three consecutively negative cervical cytology tests can discontinue testing.
  - Women with comorbid or life-threatening illness may forego cervical cancer screening.

Cervical Cancer Cytology

- Potential results include any of the following:
  - Visible/suspicious lesion on the cervix
  - A satisfactory cervical cytology/Pap test (reported using the Bethesda System 2001[173])
  - Cervical cytology/Pap test unsatisfactory
  - Cervical cytology/Pap test positive for invasive cancer
  - Abnormal cytology
    - Atypical squamous cells (ASC)
    - Undetermined significance (ASC-US)
    - Suspicion of high-grade dysplasia (ASC-H)
    - Low-grade squamous intraepithelial lesions (LSIL)
    - High-grade squamous intraepithelial lesions (HSIL)
    - Atypical glandular cells (AGC)
    - Not otherwise specified (AGC-NOS)
    - Favor neoplasia (adenocarcinoma in situ, AIS)

- Cervical cancer
- Endometrial cancer

Treatment Options Used in the Management of Abnormal Cytology

- Colposcopy is the primary method for evaluating women with abnormal cervical cytology.
  - Cervix is viewed through a long focal-length dissecting type microscope (magnification, 10–16 times).
  - A 4% solution of acetic acid is applied to the cervix before viewing, which allows for the observance of blood vessel patterns, allows a directed biopsy to rule out invasive disease, and determines the extent of pre-invasive disease.
- Loop electrosurgical excision procedure (LEEP) allows for both evaluation and treatment of abnormal cell growth on the surface tissue of the cervix. LEEP is prescribed after abnormal changes in the cervix are confirmed by Pap tests and colposcopy.
- Cold-knife conization is a procedure to obtain a sample of abnormal tissue from the cervix for further examination.
- The work-up of abnormal cytology is guided by recommendations of the American Society of Colposcopy and Cervical Pathology (ASCCP).[175] These are summarized in Table 10-1.

Biopsy Results of Abnormal Cytology

- Cervical intraepithelial neoplasia (CIN), also known as cervical dysplasia, is potentially premalignant.
  - Most cases of CIN remain stable or are eliminated by the woman's immune system, so medical treatment is not required.
  - A small percentage of cases progress to become cervical cancer, squamous cell type, if not treated.
  - The major cause of CIN is chronic infection with HPV, especially the high-risk HPV types 16 or 18.
  - The earliest microscopic change corresponding to CIN is dysplasia of the surface epithelium of the cervix.

Table 10-1: Work-up for Abnormal Pap Findings[172]

Finding	Appropriate Testing	Notes
ASC-US	Repeat Pap smear, Coloposcopy +/− HPV DNA testing	HPV-DNA positive for high-risk HPV OR repeat ASC-US findings: colposcopy
		If postmenopausal: Give intravaginal estrogen and repeat cervical cytology after treatment. If repeat is positive, then refer for colposcopy.
		If immunocompromised, refer for colposcopy.
ASC-H	Colposcopy	If normal, review cytology. If cytology confirmed as ASC-H: repeat Pap smear at 6–12 months. HPV DNA test at 12 months.
LSIL	Colposcopy	Endocervical sampling (ECC) in nonpregnant female.
		If postmenopausal: repeat testing at 6 and 12 months. Findings of ASC-US or higher require colposcopy. HPV DNA testing should be performed at 12 months. Intravaginal estrogen can be tried with repeat testing at end of course.
		For adolescents: repeat testing at 6 and 12 months. Findings of ASC-US or higher require colposcopy. HPV DNA testing should be performed at 12 months.
		If pregnant: ECC is unacceptable. Biopsies by experienced clinician highly recommended with targeted biopsies to areas of concern for invasive or high-grade disease. Repeat colposcopy should occur within 12 weeks if first unsatisfactory.

(Continues)

Table 10-1: Work-up for Abnormal Pap Findings[172] (Continued)

Finding	Appropriate Testing	Notes
HSIL	Colposcopy with ECC	If suspicious lesion present, diagnostic excision required.
		If pregnant: ECC is unacceptable. Biopsies by experienced clinician highly recommended with targeted biopsies to areas of concern for invasive or high-grade disease. Repeat colposcopy should occur within 12 weeks if first unsatisfactory with re-evaluation at least 6 weeks postpartum.
		For young women: If no evidence of cervical intraepithelial neoplasia (CIN) on biopsies, repeat colposcopy every 4–6 months for one year.
AGC NOS	Colposcopy Endometrial sampling if age >35	If normal, repeat every 4–6 months. If four consecutive negative results, return to normal testing.
AIS	Colposcopy	If negative, requires diagnostic excisional procedure.

Women who are postmenopausal, adolescent, immunocompromised, or HIV-positive have special considerations applied to their management.

- Grading of CIN
  - Cervical intraepithelial neoplasm (CIN1)
    - **CIN1** (grade I): Represents mild dysplasia and corresponds to an LSIL finding on Pap tests. It is confined to the basal one third of the epithelium.
    - **CIN2** (grade II): Moderate dysplasia confined to the basal two thirds of the epithelium.
    - **CIN3** (grade III): Severe dysplasia that spans more than two thirds of the epithelium and may involve

the full thickness. This lesion may sometimes also be referred to as cervical carcinoma in situ.

- Management of CIN is reviewed in Table 10-2.[175]

Invasive Cervical Cancer

Clinical Profile

- Grossly, invasive cervical cancer can appear in multiple ways:
  - Exophytic lesions arising from the ectocervix can be a large, friable polypoid mass. It may also arise from the endocervical canal and distend the cervix. In the literature, it is commonly referred to as a barrel-shaped lesion.

Table 10-2: Evaluation of Abnormal Biopsy Results[172]

Finding	Treatment
CIN1	Diagnostic excision OR Close follow-up (repeat colposcopy every 6 months for 1 year)
	Adolescents: Annual cytology. If HSIL at 12 months: go to colposcopy. If ASC-US at 24 months: go to colposcopy.
	Pregnant women: Follow-up only. Treatment is not indicated.
CIN2 **CIN3**	Diagnostic excision OR Laser ablation
	Adolescents: If colposcopy was satisfactory, repeat colposcopy every 6 months for up to 2 years is reasonable option. Treatment recommended for CIN3 or if CIN2 persists up to 24 months.
	Pregnant women: If early disease without invasion, repeat colposcopy is reasonable, but not less than 12 weeks in frequency. Treatment in the absence of invasion is not acceptable.
	Adenocarcinoma in situ: Hysterectomy if woman is done with child-bearing. If future fertility desired, conservative management with excision and endometrial sampling. Long-term follow-up is required.

- Infiltrating tumors present as a stone-hard cervix.
- Ulcerative lesions erode through the cervix and can involve a portion of the upper vaginal canal.

Methods of Spread

- Routes of spread of cervical carcinoma
  - Into the vaginal mucosa
  - Into the myometrium of the lower uterine segment
  - Into the paracervical lymphatics and then to involved nodes
  - Direct extension into the bladder, rectum, or parametrium
  - Nodal groups involved by cervical cancer
    - Primary nodal regions
      - Parametrial nodes
      - Paracervical or ureteral nodes
      - Obturator or hypogastric nodes
      - External iliac nodes
      - Sacral nodes
    - Secondary nodal regions
      - Common iliac nodes
      - Inguinal nodes
      - Periaortic nodes

Invasive Cervical Cancer Pathology

- Tumors of the cervix have various histological variants:
  - Epithelial tumors are the most common types of cervical cancer:
    - Squamous cell carcinoma: further characterized as (1) large cell nonkeratinizing; (2) large cell keratinizing; (3) small cell; and (4) verrucous carcinoma
    - Adenocarcinoma
    - Adenoma malignum
    - Mucinous
    - Papillary
    - Endometroid
    - Clear cell
    - Adenoid cystic
    - Adenosquamous carcinoma
    - Glassy cell carcinoma

- Tumors of mesenchymal tissue
  - Endocervical stromal sarcoma
  - Carcinosarcoma
  - Adenosarcoma
  - Leiomyosarcoma
  - Embryonal rhabdomyosarcoma
- Mesonephromas
- Lymphomas
- Melanoma
- Carcinoid

Staging

- Cervical cancer is staged using the FIGO system, which has been recently revised and adopted by AJCC.[6] Both the 1988 and 2009 staging systems are given in Table 10-3, parts (a) and (b).[176]

Table 10-3: Cervical Cancer FIGO Staging System[173]

(a) 1988 FIGO Staging System

Stage	Clinical Findings
I	Cervical carcinoma confined to the cervix
IA	Invasive carcinoma diagnosed by microscopy
IA1	Stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less
IB	Clinically visible lesion confined to the cervix
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
IB2	Clinically visible lesion more than 4.0 cm in greatest dimension

(Continues)

Table 10-3: Cervical Cancer FIGO Staging System[173] (Continued)

(a) 1988 FIGO Staging System (Continued)

Stage	Clinical Findings
II	Tumor invades beyond the uterus but not to pelvic wall or lower third of the vagina.
IIA	No parametrial invasion
IIB	Parametrial invasion
III	Tumor extends to pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis
IIIA	Tumor involves the lower third of the vagina without extension to the pelvic wall
IIIB	Tumor extends to the pelvic wall and causes hydronephrosis or renal compromise
IVA	Tumor invades the mucosa of the bladder or rectum, and or extends beyond the true pelvis
IVB	Distant metastasis

(b) 2009 FIGO Staging System

Stage	Clinical Findings
I	Cervical carcinoma confined to the cervix
IA	Invasive carcinoma diagnosed by microscopy (extension to the corpus disregarded)
IA1	Stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread.
IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less

(Continues)

Table 10-3: Cervical Cancer FIGO Staging System[173] (Continued)

(b) 2009 FIGO Staging System (Continued)

Stage	Clinical Findings
IB	Clinically visible lesion confined to the cervix or microscopic or preclinical cancers greater than Stage IA
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
II	Tumor invades beyond the uterus but not to pelvic wall or lower third of the vagina.
IIA	No parametrial invasion
IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
IIB	With obvious parametrial invasion
III	Tumor extends to pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis
IIIA	Tumor involves the lower third of the vagina without extension to the pelvic wall
IIIB	Tumor extends to the pelvic wall and causes hydronephrosis or renal compromise
IVA	Tumor invades the mucosa of the bladder or rectum, and/or extends beyond the true pelvis
IVB	Distant metastasis

- The FIGO staging system is clinically performed and allows for palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, barium enema, and X-rays.
- CT, MRI, and PET/CT are not indicated in FIGO staging of cervical cancer, though they are frequently employed in the evaluation for extent of disease.
  - CT of the chest, abdomen, and pelvis can assess the presence of distant disease and nodal metastases. Compared with clinical staging, it is more accurate in detecting advanced disease, but is not as good in determining parametrial extension of the primary tumor.[177]
  - MRI is an excellent tool for evaluation extension of disease beyond the cervix and can accurately detect 95% of stage IB or higher cancers.[177]
  - PET is superior to either CT or MRI in the detection of distant nodal metastases with a reported sensitivity of 75% and specificity of 92%.[178]
- Sentinel node biopsy has been evaluated. A French study presented at the 2009 ASCO annual meeting reported the results in a cohort of 128 patients, with 74% having a squamous cell carcinoma; 87% had stage IB disease.[179]
  - Sentinel nodes were identified in 98.4% of patients using a combined approach of radioactive technetium tracing and blue-dye labeling.
  - The sensitivity was 91.3% (95% CI 71.9% to 99%), and negative predictive value was 98.1% (95% CI 93.2% to 99.8%).
  - Sixteen percent had a positive sentinel node, though in 38% it was in an unexpected location.

Treatment

- Patients with cervical cancer may be treated with surgery or with concurrent chemotherapy. For women treated surgically, recommendations for adjuvant use of radiation with or without chemotherapy may also be present.
- Surgery includes a radical hysterectomy in most cases with pelvic and para-aortic node dissection.
  - Five types of hysterectomy procedures are described:

- Total (extrafascial) abdominal hysterectomy (type I)
- Modified radical hysterectomy (type II)
- Radical abdominal hysterectomy with bilateral pelvic lymphadenectomy (type III), which is the most commonly performed operation for stage IB cervical cancer
- Extended radical hysterectomy (type IV), which is used for tumors that involve the distal ureter or parametrium. Due to morbidity, these tumors are often referred for primary chemoradiation.
- Type V hysterectomy involves resection of a portion of the ureter or bladder.
- Complications due to radical hysterectomy[180] include: urinary tract infections (9%), fever (3.4%), and venous thrombosis (3%). Rarely, patients may have pulmonary embolism, fistula formation, ileus, lymphocyst development, or ureteral obstruction. Late sequelae include bladder dysfunction, lymphedema, and sexual dysfunction.

- Radiation therapy includes both external beam radiation (to encompass the lateral parametrial and pelvic node disease therapy) and intracavitary brachytherapy (for central pelvic disease).
  - Intracavitary brachytherapy
    - Commonly used applicator is the Fletcher-Suit intrauterine tandem and vaginal ovoids
    - Implant geometry described by Katz and Eifel[181]
    - Dose is adjusted at several pivotal points:
      - Point A: located 2 cm cephalad from the cervical os and 2 cm lateral to the uterine canal
        - Represents the medial parametrium/lateral cervix
      - Point B: 5 cm lateral to the center of the pelvis at the same level as point A
        - Focuses on the region of the obturator nodes and or the lateral parametrium
      - Point P: located along the bony pelvic side wall
        - Focuses on the external iliac lymph nodes
  - Low-dose rate (LDR) versus high-dose rate (HDR) brachytherapy

- LDR refers to traditional dosing to point A, given as 50-70 cGy/h and requiring inpatient therapy, while HDR gives a higher dose in an outpatient setting at a dose rate 200–300 cGy/min.
- In a retrospective series by Ferrigno, both approaches were compared for outcomes defined as survival, disease-free survival, local control, and late complications seen at 5 years.[182]
  - For all stages, outcomes were better for the LDR than with HDR group in terms of 5-year OS (69% versus 55%, p = 0.007), 5-year disease-free survival (73% versus 56%, p = 0.002), and local control (74% versus 65%, p = 0.004).
  - At 5 years, the rate of small bowel and urinary complications were similar between the two groups, occurring in less than 10% of patients in both arms. Rectal complications were more frequent in the group treated with HDR (8.9%) when compared to LDR (4.6%), but this was not significant.

- External beam radiation therapy
  - Used in conjunction with intracavitary radiotherapy for stage IA2 disease and above when the risk of pelvic lymph node involvement is high
  - Various techniques are utilized for planning:
    - CT simulation
    - Conformal blocking
    - Intensity modulated radiation therapy
  - Typical doses
    - External pelvic doses: 4,000–5,000 cGy followed by 4,000–5,000 cGY to point A with intracavitary LDR brachytherapy for a total dose of 8,000–9,000 cGy to point A.
    - Parametrial boost is used to complete treatment to the lateral pelvis, for a total dose to point B or P of 6,000 cGY.
- Para-aortic radiation therapy
    - Used in conjunction with external beam radiation therapy when para-aortic disease exists

- An RTOG (Radiation Therapy Oncology Group) trial noted a survival benefit in patients with stage IB greater than 4 cm, stage IIA, and stage IIB over external beam pelvic therapy alone.[183]

- Chemoradiation
  - Numerous clinical trials have reported the benefit of chemoradiation therapy in women with cervical cancer.
    - GOG 85 was a randomized comparison of hydroxyurea (HU) versus 5-fluorouracil (5-FU) infusion and bolus cisplatin as an adjunct to radiation therapy in patients with stage IIB, II, and IVA carcinoma of the cervix and negative para-aortic lymph nodes.[184] With a follow-up of 8.7 years, it showed that combined chemoradiation leads to improved survival over radiotherapy alone, 55% versus 43%, respectively ($p = 0.018$).
    - GOG 120 randomized women with cervical cancer to radiation combined with either HU as a single agent, HU, 5-FU infusion and bolus cisplatin, or single agent cisplatin.[185] It enrolled women with locally advanced disease, defined as stage IIB, III, or IVA carcinoma of the cervix and negative para-aortic nodes. It showed a benefit to platinum-based therapy over HU alone when given with radiation; OS was 64% with cisplatin alone, 66% with cisplatin/5-FU/HU, and 39% with HU alone ($p = 0.002$).
    - GOG 123 randomized women with bulky stage IB cancers to radiation therapy versus chemoradiation using weekly cisplatin.[186] All patients then had an adjuvant hysterectomy. Once more, the survival favored chemoradiation over radiation alone, 83% versus 74%, $p = 0.008$.
    - The Radiation Therapy Oncology Group ran RTOG 9001 as a comparison of pelvic radiation with concurrent cisplatin and 5-FU versus extended field radiation to include pelvic and para-aortic irradiation alone.[187] Eligible patients had stage IB to IVA cervical cancer. Concurrent chemoradiation was

associated with improved survival over radiation, 67% versus 41% ($p = 0.0001$).

- Duenas-Gonzales presented data from a randomized clinical trial of cisplatin and gemcitabine during radiation followed by two cycles of cisplatin/gemcitabine, which was tested against standard cisplatin-based chemoradiation.[188]
  - 515 women randomized in this international trial.
  - 3-year PFS significantly improved using the experimental regimen over standard treatment, 74% versus 65% ($p = 0.029$).
  - 3-year OS also supported experimental treatment, 78% versus 69% ($p = 0.022$).
  - There was a trend toward an improvement in local recurrence (11% versus 16%, $p = 0.097$), but this survival advantage appeared driven by an improvement in systemic failure rates (8% versus 16%, $p = 0.005$).
  - There were two deaths in the experimental arm; no deaths were reported in standard treatment. There was a significant increase in the number of grade 3/4 adverse events seen (215 versus 108, $p < 0.001$). Late toxicity was limited to bowel injury, reported as grade 4 in five women (2.3%) in the experimental arm, while only in one woman (0.5%) in the standard arm ($p = 0.044$).

Management by Disease Extent

- Treatment for cervical cancer is highly dependent on the extent of disease.
- Microinvasive cervical cancer is treated by hysterectomy. However, if the patient desires future fertility, surgical removal of the cervix only (trachelectomy) may be appropriate.
  - Plante et al. described the outcomes of 82 women with stage IA–IIA cervical cancer (squamous in 58%, adenocarcinoma in 42%) for whom radical trachelectomy was attempted.[189] It was successful in 72 (88%). It was abandoned in the 10 cases due to positive nodes ($n = 4$), positive endocervical margins ($n = 4$), or

extensive adhesions (n = 2). Actuarial recurrence-free survival was 95%. Tumor size over 2 cm was notably associated with a risk of relapse (p = 0.003).
  - Still, even in clinically detected early disease, standard of care is radical hysterectomy with nodal evaluation.
- Stage IB and stage II
  - Radical hysterectomy + pelvic lymph node dissection +/− para-aortic lymph node sampling is recommended.
    - Sedlis et al. reported the results of adjuvant pelvic radiation therapy versus observation in women with stage IB disease treated surgically.[190] Eligibility for this trial was at least two of three high-risk features: more than one third deep stromal invasion, lymphatic space involvement, or large tumor diameter. Comparing the radiation therapy group (n = 137) to those who did not receive further treatment (n = 140):
      - The recurrence rate was 15% versus 28%.
      - Death from all causes was 13% versus 21%.
      - This translated into a 47% reduction in the risk of relapse with adjuvant radiation therapy (p = 0.008).
      - Toxicity including grade 3/4 urologic complications (3.1% versus 1.4%), gastrointestinal complications (3.1% versus 0.8%), and myelosuppression (2.3% and 0.7%).
- Management of stage IB2 and stage II tumors
  - For locally advanced disease, primary chemoradiation using cisplatin is standard of care.
  - Alternatively, radical hysterectomy with pelvic and para-aortic lymph node evaluation can be equally considered. These patients will likely require adjuvant radiation and sensitizing chemotherapy.
    - The Southwest Oncology Group ran study SWOG 8797, which randomized women treated with radical hysterectomy and node dissection who had high-risk features to chemoradiation using 5-FU infusion and bolus cisplatin versus radiation alone.[191] High-risk was defined by the presence of positive nodes, positive surgical margins, or positive involvement of parametrial tissue.

Again, the use of chemoradiation improved survival over radiotherapy alone, 81% versus 71% ($p = 0.007$).

- Stage III/IVA disease
  - An extent of disease evaluation requires an examination under anesthesia, with a cystoscopy and proctoscopy to evaluate for bladder and/or bowel involvement.
  - Primary chemoradiation is standard of care in the absence of distant disease.
  - If technically feasible, nodal evaluation may be useful to define extension as well. This can be performed surgically or radiologically.
- Stage IVB disease
  - Disease is not curative in the context of distant metástases. Treatment is aimed to palliate and chemotherapy is often recommended. See section on metastatic cervical cancer for treatment options.
  - However, if performance status is poor, referral to hospice would be appropriate.

Adenocarcinoma of the Cervix

- Cervical adenocarcinoma is increasing in incidence each year, comprising up to 25% of all cervical cancers diagnosed in the United States.[192,193]
- This increase largely reflects the inherent difficulty in detecting glandular precursor lesions using current screening practices.
- The treatment of choice for most women with stage IA2 to IB1 disease is radical hysterectomy.
- Primary radiation with weekly cisplatin is an option for patients with stage IB2 to IIA cervical adenocarcinoma.
- Fertility-sparing surgery is an option for selected patients with adenocarcinoma in situ or stage IA1 cervical adenocarcinoma.
  - Simple hysterectomy should be performed at the completion of childbearing or when preserving fertility is not an issue.
- Patients with stage IIB to IVA disease should receive primary radiation with weekly cisplatin.

Neuroendocrine Carcinoma of the Cervix

- These are rare tumors of the cervix associated with a poor prognosis.[194]
- Current treatment regimens include surgery, radiation, and chemotherapy; a platinum/etoposide regimen is often utilized, based on extrapolation from the treatment of small cell cancers of the lung.

Surveillance of Patients with Cervical Cancer

- An interval history and physical with cervical/vaginal cytology is required every 3–6 months for 2 years, then every 6 months for 3–5 years, then annually.
- PET/CT can be helpful in diagnosis of recurrence, but its use should be guided by clinical parameters.
- Attention to issues of survivorship is also recommended. One of the more common issues is dyspareunia, related to both surgical treatment and chemoradiation. In such cases, the use of vaginal dilators and water-based lubricants can be helpful.

Recurrent Cervical Cancer

- For patients with central relapse contained within the pelvis and who have not received prior radiation therapy, surgical resection should be considered. In this case, postoperative treatment should be based on final pathology but may consist of radiation with or without chemotherapy.
- In patients with prior radiation therapy, a pelvic exenteration can be curative with 5-year survival rates between 20% and 42%.[195]
  - This procedure consists of en bloc removal of the pelvic viscera. It encompasses a radical hysterectomy, pelvic lymph node dissection, and removal of the bladder (anterior exenteration), the rectum (posterior exenteration), or both (total exenteration).[196]
  - Careful patient selection is required with most centers limiting eligible patients to those with central disease, absence of para-aortic node involvement, and without evidence of peritoneal or distant metastases.[195]

- With advances in surgical technique and pre- and postoperative care, the mortality associated with total pelvic exenteration has been reduced from 17% to 5%.[195]

Metastatic Cervical Cancer

- Therapy is not curative and the goal is palliation.
- Treatment is often complicated by
  - Prior exposure to radiation therapy that may affect blood supply to the involved field
  - Decreased bone marrow reserve
  - Advanced renal dysfunction
  - Chemotherapeutic agents have modest response rates, albeit not long lasting, which are summarized in Table 10-4.[197–203] In most trials, median OS is less than 12 months.

Table 10-4: Clinical Trials in Metastatic Cervical Cancer

Agent	Agents	Response Rate (%)	Notes
McGuire et al.[194]	paclitaxel	17	
Rose et al.[195]	cisplatin + paclitaxel	46	
Moore et al.[196]	cisplatin + paclitaxel vs. cisplatin	36 19	
Long et al.[197]	cisplatin + topotecan vs. cisplatin	*cisplatin-naive:* 39 vs. 20 *cisplatin-exposed:* 15 vs. 8	Originally designed as three arm trial with MVAC. MVAC arm stopped.
Monk et al.[198]	cisplatin + paclitaxel cisplatin + vinorelbine cisplatin + gemcitabine cisplatin + topotecan		Closed early: study arms had no difference over cisplatin + paclitaxel
Tiersten et al.[199]	paclitaxel + topotecan	59	OS 8.6 months
SCOTCERV[200]	Docetaxel + gemcitabine	26	

- Combination treatment has improved response rates though when compared to standard treatment with cisplatin/radiation, no survival advantage exists.

- Biological options
  - The antiangiogenic agent bevacizumab has been evaluated in this setting.[204] Of 46 patients enrolled, 24% were free from progression for at least 6 months. The overall response rate was 11%, all of whom had partial responses. The median PFS was 3.4 months and median OS was 7.3 months. Toxicity consisted of hypertension, anemia, vaginal bleeding, and neutropenia. There was one fatal episode of infection.
  - As of 2009, the GOG is running GOG 240, which is a randomized trial of a nonplatinum combination (topotecan/paclitaxel) versus cisplatin and paclitaxel. Patients will undergo a second randomization testing the addition of bevacizumab.[205]

Prevention

- HPV vaccines aim to eliminate preexisting noninvasive lesions (cervical intraepithelial neoplasia) by eliciting cell-mediated immunity against HPV-infected cells.
- Both the quadrivalent vaccine against HPV types 6, 11, 16, and 18 and the bivalent vaccine against HPV types 16 and 18 have been approved for use in the United States.
  - The American Cancer Society recommends its use in the following settings:
    - As routine vaccination in girls ages 11–18, though girls as young as 9 years old may begin vaccination
    - Informed discussion required regarding vaccine for women between the ages of 19 and 26
    - Boys aged 9 and older and men up to age 26 have recently been approved for vaccination in the USA using the quadrivalent vaccine.
    - Even with vaccination, girls must continue with cervical screening.
  - Two vaccines have received approval worldwide (Table 10-5).

Table 10-5: HPV Vaccines in Worldwide Use

Characteristic	Quadrivalent	Bivalent
Trade name	Gardasil	Cervarix
Manufacturer	Merck	Glaxo Smith Kline
HPV-types covered	6, 11, 16, 18	16, 18
Expression via:	Yeast	Baculovirus
Schedule	0, 2, 6 months	0, 1, 6 months
U.S. FDA Approved	Yes	Yes
Toxicity	Mild-moderate injection site symptoms (pain, swelling, redness, pruritis)	Injection site pain

- The quadrivalent vaccine targets HPV 6, 11, 16, and 18, and is marketed as Gardasil.
  - In trials, the efficacy of the vaccine was 99% at 3 years for preventing cervical intraepithelial neoplasia grade 2 and 3. However, individuals infected prior to vaccination did not appreciate the same level of efficacy (44%).[206,207]
  - The duration of immunity is not known.
- The Centers for Disease Control recently released an analysis of the vaccine adverse events (VAE) from their postlicensure surveillance program.[208] A total of 12,4242 VAE were received constituting a rate of 54 events per 10,000 doses. Serious events constitute 6% of all reports, which included 32 deaths. Common events and frequency of reporting (incidence per 100,000 doses) were:
  - syncope (8)
  - local site reactions (7.5)
  - dizziness (6.8)
  - nausea (5)
  - headache (4)
  - hypersensitivity reactions (3.1)

  - urticaria (2.6)
  - venous thromboembolism (0.2)
  - autoimmune disorders (0.2)
  - Guillian-Barre syndrome (0.2)
  - anaphylaxis (0.1)
  - death (0.1)
  - transverse myelitis (0.04)
  - pancreatitis (0.04)
  - motor neuron disease (0.009)
- Ultimately, the CDC concluded that compared with other vaccines, these rates were not greater in frequency though it was noted that there was a disproportionately high reporting of syncope and venous thromboembolism.
- A bivalent prophylactic HPV vaccine has also been tested and is marketed as Cervarix.
  - It is formulated with an immune booster called ASO4 adjuvant. This is composed of aluminum salt plus a monophophoryl lipid A, which may help induce a strong antibody response to HPV 16 and 18.[209,210]
  - In a randomized trial of over 18,000 women, vaccination was 100% effective against both incident and persistent infections with HPV 16 or 18. In the intention-to-treat analysis, vaccination was 95% effective in protection of persistent HPV 16 or 18 infections.[211]
  - In a follow-up study, protection was noted to last as long as 4.5 years.[212]

CHAPTER 11

Cancer of the Vulva

Epidemiology

- 5% of the tumors emanating from the gynecologic tract[213]
- U.S. figures: 3,700 cases with 880 deaths reported
- Incidence: 2.2/100,000

Risk Factors

- The following risk factors have been described:[214]
  - Age
    - A bimodal distribution is seen. In young women, lesions tend to be associated with HPV. In older women, they tend to develop vulvar cancers independent of HPV.
  - Increased number of sexual partners
  - History of genital warts, abnormal cervical cytology, or other HPV-associated cancers
  - Immunosuppression, either due to drugs or infection, such as HIV
  - Smoking

Symptoms

- Presenting symptoms include finding a lump, pain, or itching in the genital area.
- However, visual inspection of the vulva is required to prompt the appropriate work-up, which unfortunately is often delayed, even after signs are present.

Histologic Types

- 90% are squamous cell carcinomas
- Other tumors comprising the remaining types include:
  - Melanoma (the second most common vulvar lesion)[214]
  - Adenocarcinoma

- Basal cell carcinoma
- Sarcoma
- Undifferentiated cancers
- Metastatic lesions

Classification

- Terminology of vulvar lesions based on the 2004 International Society for the Study of Vulvovaginal Disease (Table 11-1)[215]
  - The current classification classifies vulvar intraepithelial neoplasia (VIN) into two types: usual and differentiated. It renders obsolete classification of VIN into grades 1–3, emphasizing instead biological characteristics.
  - The usual type of VIN is associated with HPV infection. It is considered the precursor lesion to invasive vulvar carcinoma.
  - The differentiated type of VIN is a high-grade lesion, which can be associated with frank squamous cell carcinoma or other dysplastic lesions. It tends to occur in older women, presenting as a unifocal lesion.

Table 11-1: Classification for Vulvovaginal Disease[212] Vulvar Intraepithelial Neoplasia (VIN)

	VIN, Usual Type	VIN, Differentiated
Typical onset	Young age	Older age
HPV-related	Yes	No
Presentation	Warty Basaloid Mixed appearance	Unifocal, as an ulcer, papule, or plaque
Association with SCC	Yes-Considered precursor lesion to invasive SCC	Can be seen with frank SCC, lichen sclerosus, or squamous hyperplasia

SCC: squamous cell carcinoma.

Staging

- Clinical detection of inguinal or femoral node involvement is difficult.
  - Physical exam has an accuracy rate of 25%.[216]
  - CT scan has a reported sensitivity of 58% and specificity of 75%, while for ultrasound alone these are 87% and 69%. If fine-needle aspiration (FNA) is added to the ultrasound, sensitivity improves to 80% and specificity is 100%.[217]
  - Pelvic MRI reported to have a sensitivity of 40% to 50% and specificity of 90% to 100%.[218]
  - Evidence of nodal involvement should prompt imaging of the chest and abdomen to rule out distant disease.
  - The FIGO staging system for vulvar cancer was recently updated. The 1998 and revised 2009 classifications are given in Table 11-2.[5]

Table 11-2: FIGO Staging System for Vulvar Cancer[5]

(a) 1998 Classification

Stage	Characteristics
I	Lesion up to 2 cm confined to vulva or perineum No evidence of nodal involvement
IA1	Stromal invasion present but up to 1.0 mm
IA2	Stromal invasion present but more than 1.0 mm
II	Tumor confined to vulva and/or perineum and more than 2 cm in greatest dimension No nodal metastases
III	Tumor of any size with (i) lower urethra, vagina, and/or anal involvement, and/or (ii) unilateral regional nodes involved
IVA	Tumor invades any pelvic structures (upper urethra, bladder mucosa, rectal mucosa, pelvic bone) and/or bilateral node involvement
IVB	Distant metastases, including to the pelvic nodes

(Continues)

Table 11-2: FIGO Staging System for Vulvar Cancer[5] (Continued)

(b) 2009 Classification

Stage	Characteristics
I	Tumor confined to the vulva
IA	Lesion up to 2 cm, confined to vulva or perineum with up to 1 mm stromal invasion, no nodal metastases
IB	Lesion **greater than 2 cm or with stromal invasion more than 1 mm; confined to vulva or perineum, with negative nodes**
II	Tumor **of any size extended to adjacent perineal structures* with negative nodes**
III	Tumor of any size with **or without extension to adjacent perineal structures*, with positive inguino-femoral nodes**
IIIA	**(i) with 1 lymph node metastasis (5 mm or larger) (ii) 1–2 lymph node metastasis (less than 5 mm)**
IIIB	**(i) with 2 or more lymph node metastasis (5 mm or larger) (ii) with 3 or more lymph node metastasis (less than 5 mm)**
IIIC	**Positive nodes with extracapsular extension**
IV	Tumor invades **other regional^ or distant structures**
IVA	**Invasion of any of the following: upper urethral and/or vagina mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone; OR ulcerated inguino-femoral nodes**
IVB	**Any distant metastatic disease, including to pelvic nodes**

*adjacent perineal structures: 1/3 lower urethra, 1/3 lower vagina, anus.
^regional areas: 2/3 upper urethra, 2/3 upper vagina.

- Prognosis is associated with disease stage. A 20-year analysis involving over 200 patients treated at the Mayo Clinic showed the OS of women with vulvar cancer was 75%.[216] By stage, Podratz et al. reported the following 5-year survival rates:
  - Stage I: 90%
  - Stage II: 81%
  - Stage III: 68%
  - Stage IV: 20%

Treatment

- VIN
  - Excision is primary treatment modality. Ablation can also be done, although it is important to ensure there is no evidence of invasion. Excised margins of 1cm or more are considered adequate.
  - CO_2 laser ablation is also an effective treatment option, with reported success rates over 90%.[219,220]
  - However, treatment, particularly of multifocal lesions, can be associated with significant postprocedure pain and healing may take a significant time.
  - The immunomodulatory agent, imiquimod, has been used as a topical agent for VIN, usual type. In a study from The Netherlands, 52 women with VIN 2/3 received imiquimod 5% cream versus a placebo, applied twice a day for 16 weeks.[221] They showed that over 80% of those treated with imiquimod had more than a 25% reduction in the size of their vulvar lesion, while no patients treated with placebo had regression ($p < 0.001$). Additionally, while nearly all patients tested positive for HPV DNA, 58% of those on imiquimod cleared HPV from their lesion versus 8% in the placebo arm ($p < 0.001$). After 12 months of follow-up, 3 of 50 had progression to invasive carcinoma (two in the placebo group versus one in the treatment arm).

Early-Stage Disease

- Historically, radical vulvectomy with inguinal, femoral, and pelvic node dissection is performed, with cure rates above 60%.[222]
  - Aim is for excision with a 1cm clear margin
  - Distal urethra can be taken with minimal affect on continence
  - Short- and long-term morbidity is significant.
    - Postoperative complication rates, including wound breakdown or infection, can be as high as 85%.[223]
    - Sexual dysfunction
    - Lymphedema
    - Generally considered a difficult surgery and often unnecessary if rate of node positivity 20% to 30%
    - Pelvic node involvement rarely seen in absence of inguinal or femoral node involvement[224]
    - Current trend is for wide local excision with macroscopic margins of 1 cm or greater
      - Compared to radical vulvectomy, no increased rate of recurrence in T1 tumors[225]
    - Sentinel node biopsy (SNB) may be a promising technique for women with early-stage vulvar cancer. Van der Zee and colleagues reported the results from a multicenter European trial in which 403 women with early disease (defined as tumor size less than 4 cm) underwent SNB, without inguinofemoral node dissection.[226]
      - Three-year recurrence-free survival among 258 patients diagnosed with unifocal disease and who had a negative SNB was 97%.
      - This was associated with far less short- and long-term complications, compared to a group who underwent completion node dissection after a positive SNB.
      - Of particular note, the rate of lymphedema was 1.9% versus 25% with long-term follow-up.[14]
    - The GOG reported the results of their vulva sentinel node mapping study, GOG 173, which sought

to determine the negative predictive value of this procedure in vulvar carcinoma.
- The study took 10 years to accrue 411 patients.
- The sensitivity was 90% (84% to 94%) with a negative predictive value of 96% (94% to 98%).
- A higher false-negative rate was noted in tumors over 4 cm. In this cohort, it was threefold higher.

- For women with positive inguinofemoral nodes, pelvic node dissection is not routinely performed. A randomized trial enrolled 114 women with inguinofemoral node-positive vulvar cancer to either pelvic radiation or pelvic node dissection.[228]
  - Estimated 2-year survival rates were 68% in those treated with primary radiation versus 54% in those undergoing pelvic node dissection ($p = 0.03$).

- Primary radiation therapy is inferior to surgery in vulvar cancer. The GOG compared groin dissection to groin radiotherapy in 58 women with T1–T3 squamous cell carcinoma of the vulva with clinically negative nodes in a randomized trial, all of whom also had a radical vulvectomy.[229]
  - At interim analysis, the study was terminated when excessive groin relapses were identified in the primary radiation therapy group.
  - Of the 25 women who underwent groin dissection, the rate of positive nodes was 20%, and these patients went on to receive postoperative radiation.
  - During follow-up, 5 of the 27 (18.5%) women treated with primary groin radiation relapsed, compared to no relapses in those treated surgically. At interim analysis, those who were treated surgically had better PFS ($p = 0.03$) and OS ($p = 0.04$).

Advanced Disease

- Advanced disease is defined as those lesions not amenable to surgical excision with grossly negative margins, those with extensive nodal involvement, or those with metastases identified beyond the pelvis.

- Ultraradical surgery, which may require exenteration, has a 4% mortality rate with only 46% disease-free survival outcomes.[230]
- Current standard of care calls for chemoradiation up front to attempt downstaging of the disease.
  - The GOG evaluated preoperative concurrent cisplatin and 5-FU with split-dose radiation therapy delivered to both the primary and the regional nodes in 46 patients with N2/N3 disease.[231]
    - Following treatment, nodal disease became resectable in 38 of 40 patients (95%).
    - At surgery, pathologic complete response was seen in 20 patients (53%).
  - In a second study, the GOG evaluated this strategy in 73 women with stage III or IV vulvar cancer.[232]
    - Following treatment, a clinical complete response was observed in 47% of patients.
    - Only 3% had residual unresectable disease.
    - The most common adverse events were surgical wound complications and skin toxicity.
- Neoadjuvant chemotherapy also remains under active investigation for women facing exenteration due to advanced vulvar cancer.
  - A study from Indiana Women's Oncology evaluated neoadjuvant cisplatin +/− 5-FU in 14 women with vulvar cancer involving the anal sphincter and/or urethra.[233]
    - All were given three to four cycles of chemotherapy prior to surgery and women on this trial received a median of three cycles of chemotherapy before undergoing surgery.
    - Of three who received cisplatin alone, no measurable response was seen.
    - Of the 10 receiving combination platinum-based therapy, at least a partial response was noted. At surgery, 2 of 14 had a complete pathologic response and all 10 patients treated with combination therapy remained disease free.
    - Of most interest, all patients receiving combination therapy had organ preservation of their anal sphincter and urethra.

Chemotherapy

- For women with advanced, recurrent, or metastatic disease, there is very little evidence to support the use of systemic treatment.
  - The GOG evaluated cisplatin 50 mg/m^2 every 3 weeks in 22 evaluable women with advanced or recurrent disease.[234] There were no objective responses seen; 45% had stable disease.
  - The EORTC reported their results using a multiagent regimen in this setting.[235] The agents used were bleomycin 5 mg IM days 1–5, methotrexate 15 mg PO days 1–4, and CCNU 40 mg orally days 5–7, each week of a 6-week cycle, which was repeated every 49 days (BMC).
    - Twenty-five patients participated (median age 66, range: 39–82).
    - The overall response rate was 56% (CR 8%; PR 48%).
    - Toxicity was predominantly hematologic.
    - However, at 8 months of follow-up, only three patients (12%) were alive.
    - The median PFS was 4.8 months and OS was 7.8 months.

Prevention

- Prevention requires early evaluation for symptoms of a lump, itching, or bleeding unrelated to menses.
- Because HPV infection is associated with an increased risk of vulvar cancer, vaccination may also be a preventative strategy.
- Joura et al. reported on the effect of vaccination against HPV 6, 11, 16, and 18 on the incidence of VIN among 18,174 women treated on one of three randomized trials of vaccination versus placebo.[236]
  - Vaccination was 100% effective in eradicating VIN 2–3 related to HPV 16 or HPV 18 and 49% against VIN 2–3 whether HPV DNA was isolated in the lesion.
  - This provides some hope that HPV vaccination will offer cross-protection against vulvar cancer, in addition to reducing the incidence and risk of cervical cancer.

CHAPTER 12

Cancer of the Vagina

Anatomy

- Tube from vulva to cervix, spanning 3 to 4 inches. The vaginal lining is comprised of squamous epithelial cells that overlie connective tissue, lymphatics, and vasculature.
- The lining is also comprised of mucus glands that allow moisture of the vaginal vault, important for normal health of the vagina and sexual function.
- The location of disease determines the pattern of nodal spread.[237]
  - Tumors of the upper vagina spread via lymphatics to involve obturator, iliac, and hypogastric nodes; tumors of the lower vagina spread to inguinal nodes first and then involve pelvic nodes.

Epidemiology

- Cancer of the vagina is a rare primary cancer of the female reproductive system. Secondary cancers are much more common, with vaginal extension from cervical cancer the most commonly diagnosed vaginal lesion.
- The American Cancer Society estimates that there will be a little over 2,000 cases each year; less than 800 women will die of their disease.[1]
- It only accounts for 1% to 2% of all gynecologic cancers in the United States[238]; worldwide, it accounts for 0.9% of all gynecologic cancers.[5]
- Prior to diagnosis of a primary vaginal tumor, it is important to exclude locally advanced lesions from other gynecologic sites, including cervical and vulvar primaries. This is especially important in women with a prior history of gynecologic cancer.

- Primary tumors in young women under 20 are generally adenocarcinomas; squamous cell carcinoma rates increase with rising age.

Risk Factors

- Brinton et al. conducted a case-control study involving 41 patients with in situ or invasive vaginal cancers and compared them to 97 community controls.[239] Risk factors identified included:
  - Low educational level
  - Low family income
  - Prior abnormal Pap smear
  - History of genital warts
  - Vaginal discharge or irritation
  - Prior trauma
- More recently, Madsen et al. evaluated risk factors in a case-control study conducted in Denmark in which 66 women with vaginal squamous cell carcinoma were compared to 164 women with cancer of the uterine corpus and 518 population controls.[240]
  - For squamous cell carcinoma, the following risk factors were identified:
    - Detectable high-risk HPV DNA
    - Prior history of cervical neoplasia
    - Poor genital hygiene
    - Tobacco smoking
    - Alcohol consumption
- A meta-analysis evaluated the prevalence and type distribution of HPV in vaginal intraepithelial and invasive cancers.[241]
  - Using PCR, HPV was detected in 100% of specimens with VAIN-1, 90% of VAIN-2, and 70% of vaginal carcinomas.

Histology

- Histologic types are given in Table 12-1.
- Vaginal intraepithelial neoplasia (VAIN)
  - This is typically diagnosed by an abnormal Pap smear in a woman previously treated by hysterectomy. It can be the initial sign of invasive carcinoma.

Table 12-1: Histologic Types of Malignant Vaginal Tumors

Squamous cell carcinoma
Keratinizing
Verrucous
Warty (aka, Condylomatous)
Adenocarcinomas
DES-associated
Clear cell
Non-DES-associated
Endometrioid
Mucinous
Endocervical
Melanoma
Sarcoma
Endodermal sinus tumor
Carcinomas (other)
Adenosquamous
Adenoid cystic
Adenoid basal
Carcinoid
Small cell
Undifferentiated

- Women are usually asymptomatic at presentation.
- Patient's history may reveal prior diagnosis of vulvar or cervical neoplasia, suggesting a "field effect" of tissue at risk[237]
- Terminology applied from that used to describe cervical intraepithelial neoplasia with classification by grade 1 through 3
  - Determination of grade based on proportion of undifferentiated cells from the basement membrane to the surface of the vagina[242]

- Undifferentiated cells involve one third or less: VAIN-1
- If more than one third but up to two thirds: VAIN-2
- If more than two-thirds thickness: VAIN-3. If full thickness involvement, the lesion is called VAIN-3, and not referred to as carcinoma in situ.

- If there is no evidence or suspicion of invasive disease, vaginal 5-fluorouracil or laser therapy has been advocated.[242]
- While vaginal estrogen has been suggested, no clinical trials are available to support its use.
- Randomized trials in this rare condition have not been undertaken.

- Squamous cell carcinoma
  - Factors reportedly associated with poor prognosis: advanced age, large tumor (4 cm or larger) and advanced stage at presentation.[243]
- Adenocarcinoma
  - Clear cell adenocarcinoma
    - Incidence is associated with maternal use of DES
    - For patients with DES exposure, peak frequency is 19 years old.
    - In utero exposure to DES is not in and of itself considered carcinogenic, but in the presence of adenosis, this exposure may be teratogenic.
    - Nodal involvement is high, even for early-stage disease. The incidence of positive nodes in women with stage I disease is over 15%.
  - Nondiethylstilbestrol-associated adenocarcinoma (NDAV)
    - Term was coined by Frank et al. In the MD Anderson Cancer Center (MDACC) experience, only 26 cases were identified over a 30-year period.[244]
      - Compared to treatment for squamous cell carcinoma (SCC), the prognosis appears worse with a 5-year OS of 34%, versus 58% of those treated for SCC ($p < 0.01$).

    - The rate of distant metastases is also worse with NDAV versus SCC, 39% versus 15%, respectively ($p < 0.01$).
- Rare histologies
  - Melanoma
    - Rare neoplasm accounting for less than 0.5% of all vaginal cancers
    - Predominantly diagnosed in the lower third of the vagina of postmenopausal women
    - Primary modality of treatment is surgical; the role of adjuvant treatment questionable at best; neither chemotherapy nor radiation therapy have been shown to be very effective
    - 5-year OS rate approximately 14%[237]
- Sarcoma
  - Leiomyosarcoma
  - Fibrosarcoma
  - Embryonal rhabdomyosarcoma
    - Most common vaginal tumor of children, with typical diagnosis in kids under the age of 5
    - Other terms: sarcoma botyroides
    - Comprised of immature skeletal muscle cells
    - Lesions tend to be multicentric
    - Treatment requires surgery followed by chemotherapy +/− radiation therapy
- Endodermal sinus tumor
  - Rare neoplasm, often presenting as a mass in the vaginas of infants or children under the age of 2
  - Other terms: mesonephroma or mesonephric carcinoma
  - Typically presents as bleeding
  - Treatment often requires a combination of surgery and chemotherapy, with small body of literature supporting use of cyclophosphamide, vincristine, and dactinomycin

Symptoms

- Nonspecific symptoms may be present:
  - Vaginal bleeding (particularly after intercourse) the most common complaint[245]

- Vaginal discharge, typically bloody
- Palpable mass
- Dyspareunia
- Other signs of advanced disease may include:
  - Dysuria (Johnson et al. reported the experience from The Ohio State University and reported that this was present in almost 25% of patients diagnosed with a primary carcinoma of the vagina.[245])
  - Constipation
  - Pelvic pain
  - Patients may not have any symptoms at all; first evidence of an issue may be an abnormal Pap smear.

Diagnosis

- Colposcopy allows direct visualization of the cervix and vaginal vault. Lugol's solution may be used to identify nonstaining areas, allowing for more targeted biopsy of any suspicious lesions.
  - Neoplastic process can involve multifocal ("skip") lesions, so comprehensive evaluation is required.

Staging

- Vaginal cancer is clinically staged using FIGO criteria (Table 12-2).[5]
- Depending on location, further exam using cystoscopy or proctoscopy may be required.
- MRI of pelvis can be used to delineate tumor borders and relation to other pelvic tissue.
- CT scan is useful to rule out distant metastases.
- Stage is biggest predictor of prognosis.[237] The 5-year relative survival by stage is as follows:
  - Stage 0: 96%
  - Stage I: 73%
  - Stage II: 58%
  - Stage III–IV: 36%

Table 12-2: FIGO Staging System for Vaginal Cancer[5]

Stage	Characteristics
0	Carcinoma in situ; intraepithelial neoplasia
I	Carcinoma is limited to the vaginal wall
II	Carcinoma extends to subvaginal tissue but not to pelvic wall
III	Carcinoma involves pelvic wall
IVA	Tumor invades bladder and/or rectal mucosa and/or directly extends beyond the true pelvis
IVB	Distant metastases

Treatment

- Therapy is dictated by extent of disease and by the patient's age. Because it is a diagnosis of older women, attention to comorbidities is also required to help individualize treatment strategies.
- Stage I lesions may be managed by upper vaginectomy (with hysterectomy if not previously performed). Pelvic lymphadenectomy is advised for the patient undergoing primary excision.
- Older patients are generally treated by primary radiotherapy. The use of chemoradiation using cisplatin has also been advocated, though in large part as a matter of extrapolation from the treatment successes for invasive cervical cancer.
- For recurrent lesions in a previously irradiated field, reexcision may require exenteration. However, the sequelae of this huge surgical procedure must be discussed; it should not be recommended or performed without significant considerations.

- Chemotherapy in the treatment of advanced or metastatic disease has no demonstrable benefit, though one trial suggested that combination chemotherapy may be beneficial.
  - Mitoxantrone was evaluated in 19 patients with either an advanced vulvar or vaginal cancer.[246] There were no responses noted and median PFS and OS was 1.6 and 2.7 months for the cohort with vaginal cancer.
  - A four-drug combination was also evaluated on protocol using methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) for advanced cervical or vaginal cancers.[247]
    - Thirty-three chemo-naive patients were treated, of which three had a diagnosis of vaginal cancer. All three patients had a response with a median duration of 12.8 months among all responders (range: 4 to 54+ months).
    - Over half of patients participating on this study had grade 3–4 neutropenia as the most common toxicity, though no deaths related to treatment were reported.
    - Although encouraging, the few vaginal cancers treated illustrates the low prevalence of the disease and the difficulty of running trials exclusive to this population.

Prevention

- Given the environmental risk factors identified in case-control studies, prevention should be aimed at reducing the rates of smoking, alcohol intake, and on prevention of sexually transmitted diseases.
- Routine surveillance is recommended as well, including vaginal inspection during pelvic examination and the regular evaluation by Pap smear.
- The role of HPV vaccination remains under investigation. A meta-analysis from De Vuyst et al. suggested that an international HPV vaccination program against HPV 16 and 18 subtypes would help prevent 60% of vaginal cancers.[241]

- Joura et al. conducted a combined analysis from three randomized trials of the quadrivalent HPV vaccine against HPV 6, 11, 16, and 18 versus a placebo and reported on the impact of vaccination on the incidence of VAIN.[236]
  - The study involved 18,174 women and reported after a median follow-up of 3 years.
  - Using an intention-to-treat analysis, it showed that vaccination was 100% effective against VAIN 2–3 caused by HPV 16 or HPV 17 and was 49% effective against these precursor lesions, irrespective of whether HPV DNA was isolated in the lesion.

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