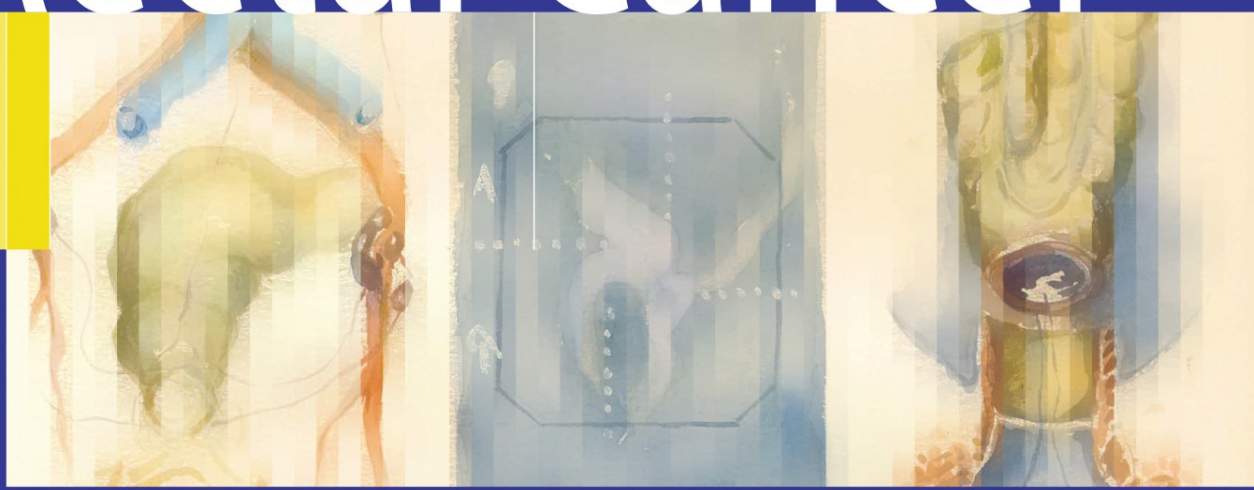
G. G. Delaini *Ed.*

Rectal Cancer



New Frontiers in Diagnosis, Treatment and Rehabilitation

Springer

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Gian Gaetano Delaini

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Foreword by
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Foreword

Twenty years ago rectal cancer was treated almost exclusively by surgery. This often took the form of total rectal excision resulting in a permanent colostomy. The quality of surgery was variable and the results were often unknown. The last 20 years have seen a remarkable transition due to various factors. Perhaps the most important was the gradual recognition that local recurrence was the appropriate end-point for local and regional treatments such as surgery and radiotherapy. Risk factors for local recurrence became identified by histopathologists and these began to be identified pre-operatively, initially by clinical examination and subsequently by imaging.

Computerised tomography, endorectal ultrasound and magnetic resonance are now capable of anticipating the pathology with sufficient accuracy to identify the degree of risk of local recurrence before treatment. This has allowed the rational development of management strategies whether they include neoadjuvant chemoradiotherapy or less invasive surgery such as local excision. Improved staging has also been at the centre of the move from excisional to restorative major surgery, with total mesorectal excision inspiring more careful dissection mindful of the locoregional pathology. While survival and freedom from local recurrence are the main end-points of treatment, function has become increasingly important as part of the measure of quality of life.

In *Rectal Cancer: New Frontiers in Diagnosis, Treatment and Rehabilitation*, all these developments are dealt with by expert authors. The editing has been uniform to create a balanced account of the areas of importance in rectal cancer as treated today. The references in each chapter are numerous and up-to-date and will be a valuable resource to the reader. There are chapters on surgical technique and choice of operation, which summarise with authority the present state of knowledge. Staging and multimodality treatment including the management of stage IV disease are dealt with in detail. Techniques to improve function by providing continence after removal of the anal sphincter and colonic reservoirs are also reviewed.

Taken as a whole, *Rectal Cancer* is an informative and accurate summary of the present position. It has focused on the areas of development and contention. The book will be a very useful contribution to the knowledge of trained practitioners and trainees alike.

R. John Nicholls

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Rectal Cancer. Epidemiology and Burden of Disease

Stefano Tardivo, William Mantovani, Emanuele Torri, Albino Poli

Introduction

It is difficult to write about the epidemiology of rectal cancer alone, to the exclusion of colon cancer, because the epidemiological data often refers to the large bowel entirely and is not separated for the two anatomical subsites [1, 2]. Consequently, in this chapter, the two cancers will be considered together. When the data is available, the rectum will be considered distinct from colon.

Although less frequent than colon cancer, rectal cancer seems to have many similar features to colon cancer in terms of geographic distribution [3]. However, some human and animal data on risk factors suggest the data cannot always be treated in the same way. Differences in some colon and rectal cancer risk factors reflect different patterns of genesis and development of rectal cancers with respect to the colon. Some modifiable risk factors that seem to be strongly associated with colon cancer are more weakly related to rectal cancer [4]. Colorectal cancer (CRC) is a serious global problem and a major public health issue. Moreover, worldwide, a great increase in social and economic burden is anticipated by changing demographics and the ageing of the population.

Assessment of the magnitude of cancer burden provides the necessary evidence for priority setting, programme planning responsive to needs, policy development within a country and an effective allocation of resources. An integrated approach that combines primary prevention, screening and treatment options represents a remarkable opportunity for public health to reduce the burden of this cancer worldwide.

Epidemiology

CRC represents, in the world, 10.5% of all cancers in men and 10.3% in women. Table 1 shows about one million new diagnosed cases with large variations between different countries. In the world, there are 1 023 152 new cases of cancer and the number of deaths per year consist of about half of all new cases (528 978). The survival profile five years after diagnosis shows a relatively favourable prognosis for CRC (Table 2), although there are strong differences between developed and developing areas, and between single countries [3, 5–16].

The developed world accounts for 65% of all new cases. Colon cancer is more common in developed countries exhibiting westernised lifestyle practices. In the world, the incidence of CRC is at the 4th position for men and at the 3rd for women (Table 3).

There are different gender patterns between colon cancer and rectum cancer. In the colon the incidences of cancer are similar for both male and female. However, there is a male predominance for rectum cancer (30–50% higher than in women).

In countries with a Western lifestyle, CRC represents the second leading cause of death from cancer (after lung cancer) for men and the third for women (after breast and lung cancers).

In developed countries (as in Northern America, Japan, Eastern, Northern, Southern and Western Europe, Australia/New Zealand), GLOBOCAN 2002 notes that approximately 665 900 people develop CRC every year and that it kills 313 900 people per year. In the less developed countries, it ranks as the seventh leading cause of death among women and fifth among men. GLOBOCAN 2002 estimates 355 700 new cases occurred in 2002 and accounted for 214 200 deaths in developing countries.

Survival rates may be due to good treatment or early diagnosis or both. Table 4 shows TNM staging (data are expressed as percentage of total for each subsite) for CRC and the 5-year survival rate for each disease stage. In the world, the prevalence of CRC, five years from diagnosis, is estimated to be about 2 800 000 subjects in 2002 [17].

As indicated earlier, CRC presents quite a big gap between different economic ranges and different countries: the highest incidence rates for both men and women are in North America, Australia/New Zealand and Western Europe (48.2, 44.4, 42.9 per 100 000 men and 36.9, 32.8, 29.8 per 100 000 women

Table 1. Incidence, mortality and age standardised rates (ASR, world standard) for colorectal cancer (2002). Data source: GLOBOCAN 2002 database available via the internet at http://www-depdb.iarc.fr/globocan/GLOBOframe.htm [Accessed 2005 March]

	New cases		ASR (W)		Deaths		ASR (W)	
	m	f	m	f	m	f	m	f
World	550 465	472 687	0.83	0.59	278 446	250 532	0.42	0.30
More developed regions	353 390	312 341	1.67	1.09	159 914	153 980	0.71	0.50
Less developed regions	196 037	159 664	0.42	0.30	118 025	96 184	0.25	0.17
Eastern Africa	4019	2997	0.25	0.17	3723	2761	0.21	0.13
Middle Africa	627	951	0.09	0.13	587	887	0.08	0.13
Northern Africa	3150	2707	0.21	0.17	2935	2525	0.17	0.13
Southern Africa	1553	1644	0.46	0.38	1056	1106	0.30	0.25
Western Africa	3430	2605	0.21	0.13	3224	2460	0.17	0.13
Caribbean	2610	3032	0.59	0.63	1633	1945	0.38	0.38
Central America	3677	3870	0.30	0.29	2136	2310	0.17	0.17
South America	22 159	24 125	0.67	0.59	10 936	12 147	0.33	0.29
Northern America	94 745	88 728	1.84	1.34	33 421	32 939	0.63	0.46
Eastern Asia	155 157	107 578	0.80	0.50	75 281	56 250	0.38	0.25
South-Eastern Asia	23 760	21 119	0.50	0.38	15 063	13 362	0.33	0.25
South-Central Asia	26 940	20 254	0.17	0.13	18 248	13 525	0.13	0.09
Western Asia	7544	7226	0.46	0.38	4583	4370	0.26	0.21
Central and Eastern Europe	55 408	56 814	1.25	0.83	36 602	38 597	0.80	0.51
Northern Europe	29 102	26 213	1.55	1.09	13 999	13 483	0.71	0.50
Southern Europe	43 586	35 575	1.46	0.96	21 661	18 163	0.71	0.46
Western Europe	64 886	60 122	1.76	1.21	29 968	30 823	0.79	0.58
Australia/New Zealand	7897	7002	2.00	1.51	3247	2786	0.79	0.58
Melanesia	149	78	0.30	0.17	101	54	0.21	0.09
Micronesia	30	22	0.63	0.46	19	14	0.38	0.30
Polynesia	31	26	0.59	0.42	20	18	0.38	0.29

Table 2. Estimated age-adjusted colorectal cancer survival (%) by country/area

	5-year survival (%)	
	Males	Females
United States	66	65
Eastern Europe	35	36
Western Europe	56	53
Japan	65	58
All developed areas	**56**	**54**
South America	50	50
India	28	31
Thailand	37	37
Sub-Saharan Africa	13	14
All developing areas	**39**	**39**

respectively), while the lowest rates are registered in Central and Western Africa, and in South Asia (2.3, 5.1, 4.7 per 100 000 men and 3.3, 3.5, 3.5 per 100 000 women respectively) (Fig. 1).

There is even a variation for the site of the neoplasm (colon/rectal). In fact, in "high-risk countries", 2/3 of all cases are represented by a colon cancer and 1/3 by a rectal one [17]. In contrast, in "low-risk countries", the risk for the two sites is the same. The incidence variation in different sites could be explained by different exposure to risk factors. There is a direct correlation between CRC and diets high in red meat, animal fats, alcohol and a low use of fibre. Some epidemiological studies note that a sedentary life and excess body weight can increase the risk of CRC.

Research evidence reveals that the incidence in groups of migrants from low to high risk countries tends to increase to the rates of the host countries within the first or second generation, or, even as early as within the migrating generation itself. The geographic location of the country of origin, age at migration, time of residence in the adoptive country and the extent of cultural assimilation all influence the level and speed of the increase. There are several examples of this such as the mortality of Japanese immigrants in the United States, which is significantly higher than that among the Japanese in Japan [18, 19]; and by the early 1970s the Japanese in Hawaii had a mortality similar to that of whites in Hawaii [20, 21]. Also, in Chinese people migrating to the USA, mainly from one province in China, the mortality rate among the first generation of migrants was 2.7–5.6 times higher than found in that province [22, 23].

Table 3. Incidence (new cases) by sex and cancer site worldwide, 2002

Males	No. of new cases	Females	No. of new cases
Lung	965 241	Breast	1 151 298
Prostate	679 023	Cervix uteri	493 243
Stomach	603 419	Colon/rectum	472 687
Colon/rectum	550 465	Lung	386 891
Liver	442 119	Stomach	330 518
Oesophagus	315 394	Ovary	204 499
Bladder	273 858	Corpus uteri	198 783
Oral cavity	175 916	Liver	184 043
N-H lymph.	175 123	Oesophagus	146 723
Leukaemia	171 037	Leukaemia	129 485

Another example describes the incidence differences in Israeli Jews according to place of birth [24]:
- in Europe or America (22.5/100 000),
- in Israel (18.1/100 000),
- in Africa or Asia (13.2/100 000),
- as well as, in Israeli non-Jews (4.6/100 000).

About 20–30% of all large bowel cancers are in the rectal site, 20–26% in the sigma, 10% in the descending colon, 13% in transverse colon and 15–20% in the proximal colon (ascending colon and appendix).

Subsite distributions of colorectal malignancies indicate that approximately 70% of colorectal malignancies are localised in the distal or left large bowel (between the splenic flexure and the lower rectum) [25]. Several studies, however, showed a tendency for a shift to proximal sites of cancer distribution, with right-sided cancers becoming more prevalent and left-sided lesions less prevalent [26–30]. These studies are not without controversy [31, 32]. If the "rightwards shift" is a true phenomenon, this might represent one more reason for abandoning sigmoidoscopy and favouring pancolonoscopy as the technique of choice for screening individuals at risk of CRC.

It remains unclear if this is a true biological phenomenon or simply an artefact due to a variety of factors including the lack of agreement on the most appropriate division of the colorectum into anatomical subsites [1, 2]. Other possible explanations for the different distribution pattern of colorectal malignancies into right and left colonic segments might include: the impact of environmental risk factors such as diet and lifestyle, a different frequency of hereditary colorectal neoplasm (which are characterised by an increased frequency of right-sided lesions) [33] and a more or less extensive use of colonoscopy.

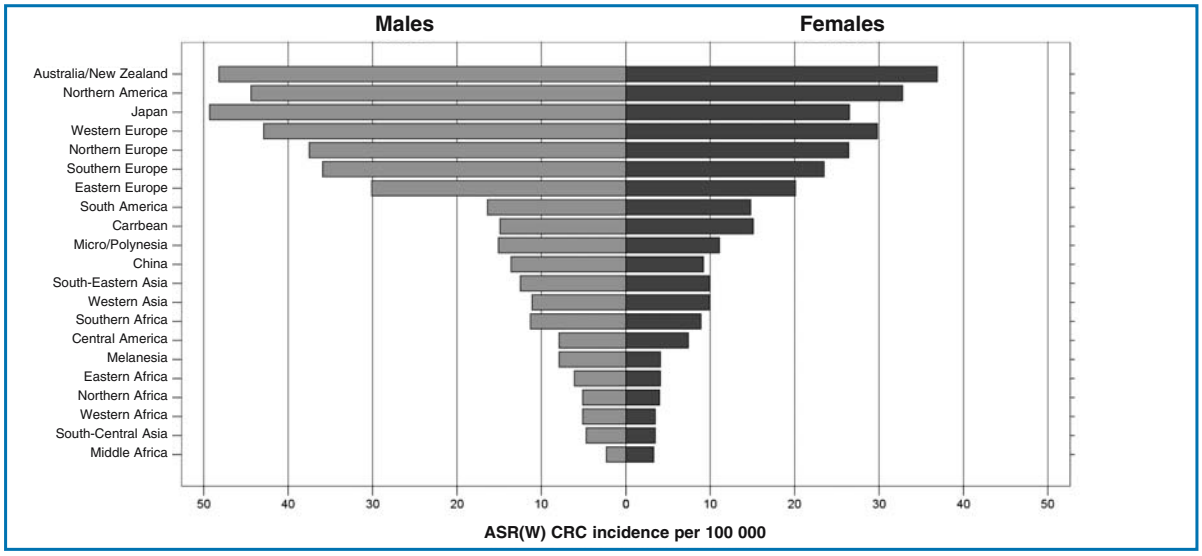

Fig. 1. Age standardised (world population) incidence rates for colorectal cancer. Data shown per 100 000 by sex. Data source: GLOBOCAN 2002 database available on the internet at http://www-depdb.iarc.fr/globocan/GLOBOframe.htm [Accessed 2005 March]

In a recent study Ponz de Leon et al. [34] examined the pattern of incidence, subsite distribution and staging in the 15-year experience of a specialised cancer registry (Modena, Italy). They found that:

1. There was a general increase in the incidence of colorectal neoplasms during the registration period. This increase was observed in both sexes, though incidence rates in women remained significantly lower than in men.
2. Tumours were appreciably more frequent over the age of 50 years.
3. Tumours stage I, II and III showed a significant increase in incidence over time (with a significant improvement of 5-year survival). In contrast, the incidence of more advanced disease (stage IV) remains quitestable.
4. There was a gradual increase in cancer incidence in all colonic segments, while rectal lesions tended to decline.

The more favourable staging at diagnosis is presumably related to the wider use of colonoscopy. This, in turn, can be attributed to an increased attention of patients and doctors towards the screening and early detection of this common neoplasm.

Burden of Disease

CRC is the fourth most common cancer in the world with approximately 1 000 000 new cases per year worldwide (GLOBOCAN 2002). CRC accounts for 10% of all cancer. North America, Australia/New Zealand and Europe are considered to be high-risk areas. Colon cancer is more common in developed countries exhibiting westernised lifestyle practices.

In general, the incidence of CRC is increasing rather rapidly in countries where the overall risk was formerly low (especially in Japan, but also elsewhere in Asia). In high-risk countries, the trends are either gradually increasing, stabilising (North and West Europe) or declining with time (North America). Such changes over time have been noted particularly in younger age groups [3, 7, 17, 35].

CRC is not perceived as a significant health problem in developing countries, where infectious disease and perinatal and maternal mortality have usually received more attention. However, once an individual has survived the first five years of life, cancer becomes one of the major causes of death in developing countries [36]. The slow, but progressive, extension to developing countries of western culture and the ageing of the population will lead to an increase in the incidence of the neoplasm in these countries.

In the last few decades, the increase has been more relevant in Eastern than in Western populations. The incidence of CRC in the Czech Republic is one of the highest in Europe and the incidence of rectal cancer is the highest in Europe in both male and females [9, 13, 15, 37–40].

Even if the age-specific mortality rates remain constant between 2000 and 2004, there will be an increase in the absolute number of cancer cases and deaths in the foreseeable future. Although the total population will remain fairly constant, compared with 2000, by 2015 there will be a 22% increase in the population aged ≥65 years and a 50% higher number of persons aged ≥80 years [38]. Given the association between CRC risk and age, this will lead to a major increase in the cancer burden [41].

Analysis of trends in all cancer mortality in Europe over the past 30 years has shown that after long-term rises, age-standardised mortality from most common cancer sites has fallen in the European Union since the late 1980s. In the 1980s, the 12 member-countries of the European Community set the ambitions target to reduce cancer mortality from 15% between 1985 and 2000. The actual overall decrease was 10% in men and 8% in women [42]. The target was met only in Austria and Finland, for both men and women; in Luxembourg and the UK there were 15% reductions in men, but not in women. In Greece and Portugal there was an increase in the numbers of cancer deaths in both sexes.

Cancer incidence can measure the effect of primary prevention but not of early detection. The latter may cause an increase in incidence, which occurred in several countries using breast screening mammography. The aim of early detection is to improve survival. Cancer mortality reflects the combined effects of changes in incidence and survival [38].

Rising trends in risk of dying from CRC are present in the majority of European Union member states and there are particularly strong trends in increasing risk in Spain, Portugal and Greece [41].

Interestingly, there has been a striking decline in CRC in women compared with men. This may in part be due to the increasing penetration of oral contraceptives and, particularly, hormone replacement therapy (HRT) [43], both of which have consistently been associated with a decreased risk of CRC. However, this may be sheer speculation. There has been an overview of all the case-control and cohort studies investigating this association separately for oral contraceptive and HRT users. Overall, the risk of CRC in users of oral contraceptives (compared with never-users) was reduced by 18% [RR=0.82, 95% confidence interval (CI) 0.74–0.92] [44]. For HRT, the risk of CRC was reduced, overall, by 20% among users compared with non-users (RR=0.8, 95% CI 0.78–0.82) [45].

Screening for CRC has been shown to be effective [42]. The introduction of organised screening pro-

Table 4. Staging (% of total) and 5-year survival of colorectal carcinoma, by anatomical sub-localisation

UICC	Disease stage at time of diagnosis		5-year survival rate %	
	Colon	Rectum	Colon	Rectum
I	10–12	20	75–100	78–93
II	35–40	25–30	50–60	40–60
III	20–25	20–30	15–40	15–33
IV	18–20	12–20	0–5	0–5
Unknown	6–8	13	–	–

grammes throughout Europe will lead to a reduction in CRC mortality. The maximum effect will be derived from programmes with effective quality control procedures in place.

CRC, with an estimated 376 400 new cases and 203 700 deaths in 2004, remains an important public health problem in Europe. Even if age-specific rates remain constant, the ageing of the European population will cause these numbers to continue to tise.

In its Annual Report, the American Cancer Society estimates that, in 2005 in the United States, about 145 290 people will be diagnosed with CRC, and that about 56 290 people will die from this disease [46]. In the United States, CRC is the third most common cancer both for men and women. The incidence ranks second to breast cancer for Hispanic, American Indian/Alaska Native and Asian/Pacific Islander women, and ranks third for white and black women [14]. The overall incidence increased until 1985, then began to decrease steadily at an average rate of 1.6% per year. For women, mortality rates have been declining since at least 1950, while rates for men remained fairly level from 1950 to 1980, but then began declining in the 1980s. The five-year relative survival rate for CRC was 61% and varied by stage. When CRC was detected in the earliest stage of the disease, Stage I, the survival rate was 96%, whereas survival for Stage IV was only 5%.

The Authors of the report suggested that screening and advances in treatment helped to reduce mortality from the disease. They also found that incidence and mortality varied somewhat from state to state. Incidence and mortality among African Americans was higher than in other racial and ethnic groups, a disparity which could possibly be reduced in the future through better screening utilisation and access to care.

From 1990 to 1994 the survival rate of subjects with rectal cancer in Europe was 75% at one year and 47% at five years. The five-year relative survival rate declined with age: from 55% in the youngest (45–54 years) to 39% in the oldest age group of patients (75 years and over) [40, 47]. There have been consistent improvements in the survival rate since the late 1970s in both sexes and in all regions of Europe. In Europe as a whole, survival rates rose by 7% for both one and five-year survival [40]. The survival curves for rectal cancer differ in shape from colon cancer. The one-year survival rate from rectal cancer is higher than colon cancer (75 *vs.* 70%), but the five-year survival rate is similar (Table 4).

In the United States, the 5-year survival rate for patients diagnosed with cancer of the rectum during 1985–89 was 57%, while in Europe the figure was 43% [5]. Rectal cancer is characterised by a much better response when treated at an early stage. The large survival differences may therefore, reflect the fact that more healthy Americans than Europeans undergo early diagnostic procedures. An indicator of early diagnosis is the proportion of CRCs that are diagnosed as adenocarcinomatous polyps; this figure was much higher among American cases than in European cases (13% *vs.* 2%) [12].

The EUROCHIP study demonstrated that CRC patients' incidence and survival depends on socioeconomic factors including access to and quality of medical care [48]. In the EUROCHIP study, gross domestic product (GDP), total (public and private) health expenditure (HE) and longer survival rates in CRC were significantly correlated, indicating that the availability of resources can influence the clinical outcomes (Fig. 3).

In fact, in these countries, with lower GDPs and HEs, there are also lower incidence and mortality rates for CRC. In Italy, it is lower yet again by a 5-year survival percent (Figs. 2–4 and Tables 5, 6). In countries with a GDP lower than 10 000 PPP$ (parity of purchasing power in US $) per capita such as Mexico, Venezuela, Botswana, Mauritius and the Dominican Republic, the incidence of new cases of CRC, both in men and women, is around 0.30 and 0.50 for every 100 000 people/year. On the other hand, countries with a GDP of more than 20 000 PPP$ per capita have, except for Finland, an age-standardized rate (ASR) incidence for CRC higher than 1.40 new cases for 100 000 people.

It is possible to suppose the existence of a direct relation between the number of new cases of CRC and the GDP per capita (ASR incidence and GDP per capita: correlation coefficient 0.63; $p<0.0001$; ASR

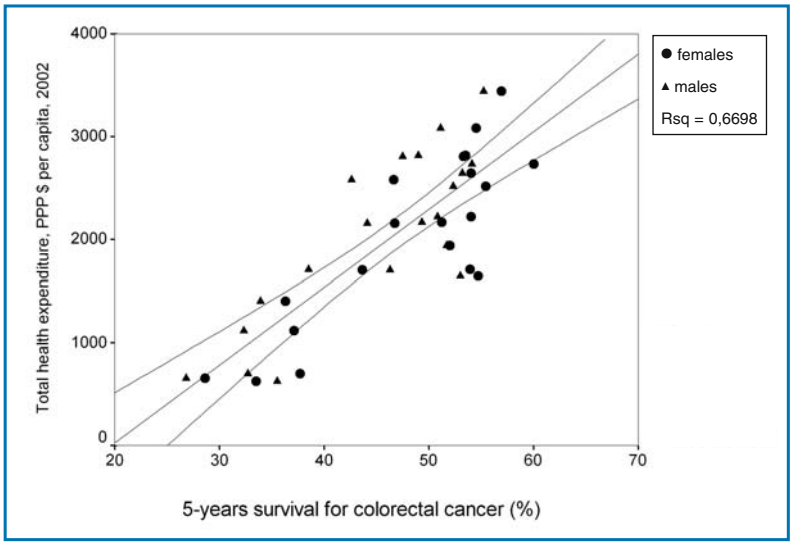

Fig. 2. Five-year survival for colorectal cancer and total health expenditure (HE) PPP US $ per capita (2002). Correlation coefficient 0.81; $p<0.0001$; $R^2=0.67$

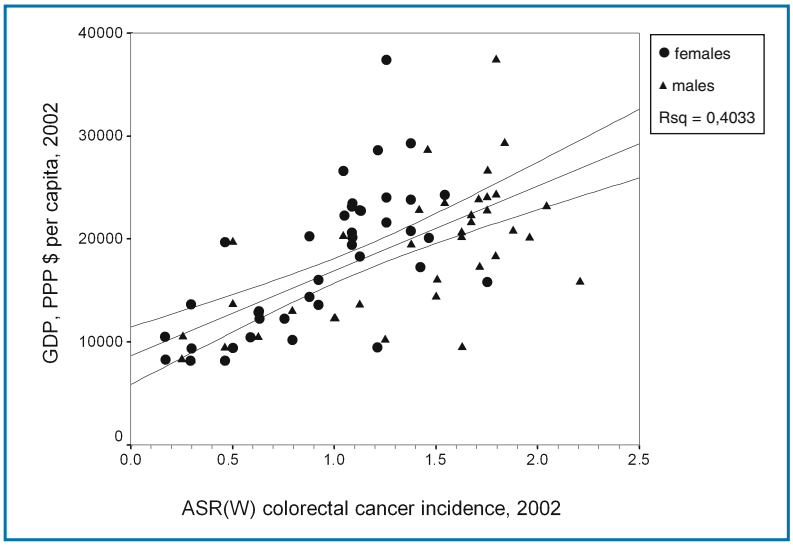

Fig. 3. Age standardised (world population) incidence rates for colorectal cancer and gross domestic product (GDP) PPP US $ per capita (2002). Correlation coefficient 0.63; $p<0.0001$; $R^2=0.40$

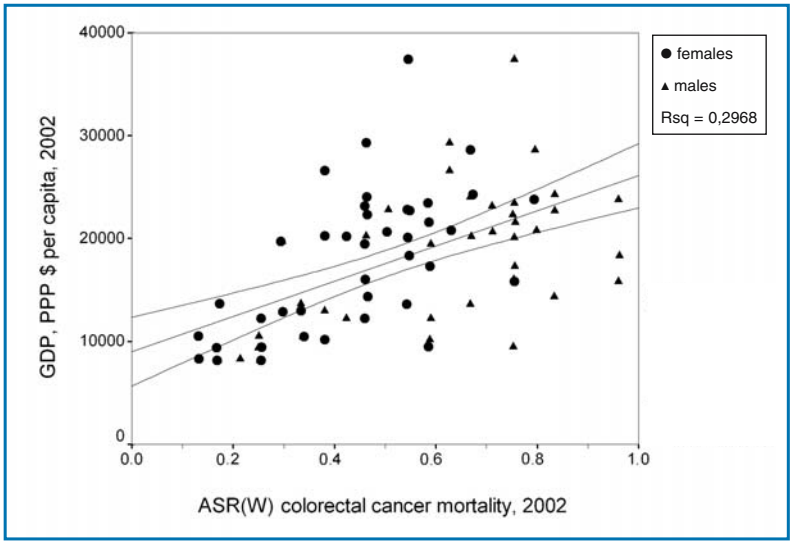

Fig. 4. Age standardised (world population) mortality rates for colorectal cancer and gross domestic product (GDP) PPP US $ per capita (2002). Correlation coefficient 0.54; $p<0.0001$; $R^2=0.30$

Table 5. Incidence and mortality age standardised rate (ASR) per 100 000 for colorectal cancer and gross domestic product (GDP) PPP US $ per capita (2002) in different countries

Country	GDP	Incidence ASR (W)		Mortality ASR (W)	
		M	F	M	F
Mexico	8190	0.30	0.29	0.17	0.17
Venezuela	8190	0.46	0.46	0.25	0.25
Botswana	8310	0.25	0.17	0.21	0.13
Mauritius	9400	0.50	0.30	0.25	0.17
Dominican Republic	9440	0.46	0.50	0.25	0.26
Uruguay	9480	1.63	1.21	0.75	0.58
Argentina	10 200	1.25	0.79	0.59	0.38
Bahamas	10 460	0.63	0.59	0.34	0.34
Madagascar	10 530	0.25	0.17	0.25	0.13
Barbados	12 260	1.00	0.75	0.59	0.46
Korea, Republic	12 270	1.00	0.63	0.42	0.25
Chile	12 890	0.63	0.63	0.30	0.30
Greece	13 010	0.79	0.63	0.38	0.33
Malta	13 610	1.13	0.92	0.67	0.54
Bahrain	13 700	0.50	0.29	0.33	0.17
Portugal	14 380	1.50	0.88	0.83	0.46
New Zealand	15 840	2.21	1.75	0.96	0.75
Spain	16 060	1.51	0.92	0.75	0.46
Israel	17 310	1.71	1.42	0.76	0.59
Ireland	18 340	1.79	1.13	0.96	0.55
Sweden	19 480	1.38	1.08	0.59	0.46
United Arab Emirates	19 720	0.50	0.46	0.30	0.29
Australia	20 130	1.96	1.46	0.75	0.54
Italy	20 200	1.63	1.09	0.67	0.42
Finland	20 270	1.05	0.88	0.46	0.38
United Kingdom	20 640	1.63	1.09	0.71	0.50
Germany	20 810	1.88	1.38	0.80	0.63
The Netherlands	21 620	1.67	1.26	0.76	0.59
France	22 320	1.67	1.05	0.75	0.46
Austria	22 740	1.75	1.13	0.83	0.55
Iceland	22 830	1.42	1.13	0.51	0.54
Japan	23 180	2.04	1.09	0.71	0.46
Belgium	23 480	1.54	1.09	0.75	0.58
Denmark	23 830	1.71	1.38	0.96	0.79
Canada	24 050	1.75	1.25	0.67	0.46
Norway	24 290	1.79	1.54	0.83	0.67
Switzerland	26 620	1.75	1.04	0.63	0.38
Singapore	28 620	1.46	1.21	0.80	0.67
United States of America	29 340	1.84	1.38	0.63	0.46
Luxembourg	37 420	1.80	1.26	0.75	0.54

mortality and GDP per capita: correlation coefficient 0.54; $p<0.0001$).

The same figure is shown considering the age-adjusted 5-year survival rate and the HE. And, in fact, there is a direct relation between the survival rate 5 years from diagnosis of CRC and the HE (correlation coefficient 0.82; $p<0.0001$).

The association between fiscal input and clinical outcomes should be taken into account for the development of effective public health. It can be argued that larger investments must translate into greater primary and secondary prevention and specialised care.

Risk Factors

The study of risk and protective factors can help to quantify the proportion of the cancer burden explained by known causes and to estimate the avoidable cases or deaths. Many factors have been postulated as either determinants of CRC or increasing its risk. The possible analysis of risk factors suffers from the same shortcomings of analytical epidemiological studies investigating the complex issues of diet and lifestyle [49, 50].

Not all identified causes of CRC are, of course, equally modifiable. A distinction must, therefore, be

Table 6. Age-standardised 5-year survival (%) after diagnosis (colon and rectum cancer and colorectal cancer) and total health expenditure (HE) PPP US $ per capita in 2002 in different countries

Country	HE	5-year survival rate					
		Colon cancer		Rectum cancer		Colorectal cancer	
		M	F	M	F	M	F
Estonia	625	38.0	37.0	32.5	28.2	35.5	33.5
Poland	654	26.3	28.7	27.3	28.5	26.8	28.6
Slovakia	698	39.9	43.7	26.1	31.2	32.7	37.7
Czech Republic	1118	38.1	36.4	26.8	38.2	32.3	37.1
Slovenia	1405	34.8	38.8	33.0	34.0	33.9	36.3
Spain	1646	55.0	55.8	50.0	52.5	53.0	54.7
Portugal	1702	49.0	43.5	42.7	44.1	46.3	43.6
Malta	1709	35.9	53.3	39.6	57.2	38.5	53.9
Finland	1943	54.0	52.7	49.3	50.8	51.7	52.0
United Kingdom	2160	45.3	47.2	42.0	45.5	44.1	46.7
Italy	2166	51.2	52.1	46.0	48.9	49.3	51.2
Austria	2220	55.1	58.4	44.2	46.1	50.8	54.0
Sweden	2517	52.2	54.4	52.4	57.1	52.3	55.4
Denmark	2580	43.2	47.6	41.8	44.6	42.6	46.6
The Netherlands	2643	51.9	54.0	55.2	53.9	53.2	54.0
France	2736	55.9	58.7	51.5	62.3	54.1	60.0
Iceland	2807	45.9	55.2	–	49.0	47.5	53.3
Germany	2817	50.5	54.5	46.9	51.5	49.0	53.5
Norway	3083	51.4	53.6	50.6	56.2	51.1	54.5
Switzerland	3445	55.0	56.3	55.8	57.3	55.2	56.9

made between "identified not avoidable" causes of cancer and "avoidable" causes of cancer. There is no clear line between environmental identified causes and avoidable causes. We do not have a clear line between the two, as it depends on the extent to which we consider environment, health behaviour and, in general, external modifiable factors.

CRC is a multifactorial disease in which pathogenesis plays a role as well as inherited predisposition and environmental factors. Epidemiological evidence suggests that diet and other environmental factors may have a major impact on incidence variations among countries and the global burden of the disease [51–53]. In Europe and the United States, up to 5% of the general population may develop this cancer by the age of 75 [54].

CRC is sporadic when it has not been evidenced that there is a predisposition to the disease and, thus, the individual does not carry a high-risk mutation. CRC is regarded as "inherited", when there is a clear genetic transmission in familial pedigree, while it is considered "familiar" if there is a number of persons affected in a family with a proportional risk increase. Approximately 75% of CRCs are sporadic and develop in people with no specific risk factors. On the other hand, 25% of all these cancers occur in people with significant risk factors, most of which, 15–20%, develop in people with either a positive family history, a personal history of CRC or polyps. The remaining cases occur in people with genetic predispositions such as hereditary non-polyposis CRC (HNPCC, 4–7%), familial adenomatous polyposis (FAP, 1%) or in people with inflammatory bowel disease (1%) [55].

Non-Avoidable Risk Factors

Certain differences in sex incidence emerge when carcinomas are assessed separately for the large bewed. Right colon lesions have been observed to be more common in women while men seem to be at higher risk for rectal cancer. The prevalence of colon cancer has a ratio of females/males equal to 1.2:1, and rectal cancer a ratio of males/females equal to 1.4:1. Right colon cancers have been shown to account for a greater percentage of colorectal neoplasms in older patients while left colon and rectum neoplasms seem to appear in relatively younger patients [56].

CRC is slightly more common in females before the age of 60, but thereafter it predominates in males [57, 58].

The risk of CRC increases as people get older. Age is the most important risk factor for both colon and rectal cancer. There is a peak of incidence in subjects aged 60–69 years. Only 3% of all cancers develop in persons under 40 years [59]. There is a sharp rise in the incidence of CRC between 40 and 50 years, and

the number of people affected is even higher over the age of 50 years. Everyone above 50 can be considered at medium risk for the disease.

Genetic factors appear to influence the age of onset of CRC. Early onset of cancer is seen in hereditary conditions like FAP and HNPCC. The mean age of diagnosis is in the early 30s for FAP [60] and in the 40s for HNPCC [61]. First degree relatives of patients are estimated to have an average onset of cancer 10 years earlier than people with sporadic cancer. Knowledge of age is important to address screening strategies for average- and high-risk groups.

The populations of Western nations tend to have a higher incidence of CRC than developing countries, or Asian and African populations. However, it appears that ethnic and racial discrepancies are not very relevant. Migrant studies suggest that when ethnic and racial discrepancies exist, environmental factors play a major role. In the United States, today, the risk seems to be stronger for African Americans [62]. African Americans have a higher rate of proximal cancer compared to Caucasians, who have higher rates of distal and rectal cancer [63].

Among other factors, tall adult height, which is partly determined by sufficient nutrition in childhood and adolescence, could be associated with increased risk [64].

The hypothesis that the development of CRC (both sporadic and familial inherited forms) is from premalignant lesions, and particularly large adenomatous polyps, is widely accepted [65, 66].

The development of CRC is a multistep process that involves some genetic changes [67]. About 85% of all CRCs are due to events resulting in chromosomal instability and the remaining 15% are due to microsatellite instability [68]. Specific genetic mutations, inherited as autosomal dominant, have been identified as the cause of inherited colon cancer risk in prone families.

The first group of heritable syndromes is represented by familial polyposis syndromes. The most important, and best known [69] is FAP, which involves the early onset of pancolon adenomatous polyps. A less severe form is known as attenuated familial adenomatous polyposis [70]. Polyps in FAP are not present at birth, but have developed by late adolescence. The condition is characterised by hundreds of polyps (500–2500). A minimum of 100 is needed for the diagnosis of FAP. This syndrome affects approximately 1 in every 8000 individuals. Without intervention, virtually all patients develop CRC. A variant of FAP is Gardner syndrome. It is inherited as an autosomal dominant trait, which occurs with half the frequency of FAP [67]. In affected individuals, the entire large and small bowel may present adenomas. This syndrome is accompanied by mesenchymal abnormalities, and tumours may coexist as: lipomas, fibromas, osteomas, sebaceous cysts and desmoid tumours. Other very rare syndromes, probably with the same genetic defect [68], are Oldfield's syndrome and Turcot's syndrome. In Oldfield's syndrome (multiple sebaceous cysts, polyposis and adenocarcinomas) [71] and Turcot's syndrome (malignant central nervous system tumours and bowel polyposis) [72], polyps arise within 10–20 years and CRCs follow after 10–15 years.

The second group of heritable syndromes includes HNPCC syndromes. A strong family history of CRC is present at an early age for individuals classified as HNPCC [73]. HNPCC syndromes, inherited as an autosomal dominant trait, have been subdivided into the Lynch I and II syndromes [74]. In Lynch I syndrome, where the colon is more frequently involved than the rectum, the development of multiple colon cancers occurs at an earlier stage (and earlier age) than expected in sporadic CRC. A more generalised condition, Lynch II syndrome is always inherited as an autosomal dominant condition and has been described for families with multiple colon and extracolon adenocarcinomas (familial adenocarcinomatosis). Colorectal malignant neoplasia is associated with cancers of the ovary, pancreas, breast, bile duct, urinary ways, stomach, and frequently, of the endometrium [75]. The diagnosis of HNPCC is based on the Amsterdam criteria: CRC present in three or more family members, two generations affected, a patient who is a first-degree relative of another affected person and a cancer diagnosis before the age of 50 [76].

Other hereditary syndromes like juvenile polyposis and Peutz-Jeghers syndrome have also been linked to an increased risk of CRC [77, 78].

A family history of colon carcinoma is another significant clinical risk factor [79–81]. In this case, it has been demonstrated that there is a threefold increased risk. The relative risk of developing this malignancy when one first-degree family member is affected is 2.3; while with two first-degree family members affected the relative risk increases to 4.3. If the first-degree family member is younger than 45 years at the time of diagnosis, the relative risk rises to 3.9 [82].

Patients with a personal history of colorectal carcinoma are at greater risk of developing a second colorectal malignant neoplasia. A history of colorectal polyps can determine a higher risk of cancer. It has been found that the cumulative risk of cancer developing in a 'not removed polyp' is 3% at 5 years, 8% at 10 years and 24% at 20 years after the diagnosis [83]. It should be noted that adenomas may be larger and more numerous in subjects without HNPCC or FAP but with a strong family history of CRC [84]. There are other individual clinical condi-

tions that can increase susceptibility to CRC. An increased risk for CRC has been confirmed in patients with inflammatory bowel disease of significant duration (8–10 years). Ulcerative colitis is more strongly associated with cancer than Crohn's disease. The incidence of malignancy seems to augment with the extent of bowel involvement and with the severity and duration of the disease [85, 86]. The risk of carcinoma is increased with the duration of colitis; it has been estimated to be more than 30% in the third decade of the disease [87]. Other clinical risk factors are a history of pelvic irradiation and non-cancer surgery. Pelvic radiotherapy, which involves mostly women treated for gynaecological neoplasms, can be relevant to the risk of rectal cancer [88]. Some evidence suggests that patients who have undergone cholecystectomy [89] and ureterosigmoidostomy [90] may have an increased chance of CRC too. A history of breast, endometrial or ovarian carcinoma [91] and no or low parity have been linked to higher risk of CRC among women [92].

Avoidable Risk Factors

A comparison of CRC rates in different countries shows great variation. And time trends within some countries are also notable. Dietary, lifestyle and environmental factors but not racial, ethnical or genetic factors seem to account for a great part of the differences in incidence. Some of the most striking, rapid and well documented changes in diet were seen in Japan [93]. Consumption of meat and dairy products increased between the 1950s and 1990s and thus the rate of CRC [4]. Changes in food habits have been shown in western countries [94], but also in developing countries such as China [95]. Moreover, the observation that CRC in migrants from low-risk populations eventually rises to equal the rates of the new host population supports the hypothesis that exposure to environmental factors may be important in the aetiology of the disease.

Data on Japanese (with low incidence in native country) first-generation migrants to Hawaii confirmed a strong augmentation in colon cancer risk similar to whites living in Hawaii [96]. Relevant incidence increases have been well documented for Puerto Ricans emigrating to the United States [97] and also for migrants from Poland to the United States and Australia [98].

Higher CRC rates in industrialised countries could be related to diets rich in animal products, red meat, animal fats and proteins, and refined sugar, and low in plant-based foods. On the other hand, low-risk diets in developing countries have been observed to be richer in vegetables (particularly cruciferous), protein from vegetable sources, fibre, whole grains and fruits [99]. The protective effects of a plant-based diet could be due to some components like fibre, vitamins, mineral, antioxidants and phytochemicals.

The negative impact of an animal-based diet has been attributed to saturated fats, meat protein, excessive caloric intake and the scarce presence of protective foods [100]. Low-risk diets include the traditional Mediterranean and Asian diets. It has been suggested that major developed countries could reduce their incidence of CRC by switching from a western diet to a Mediterranean diet [101]. The effects of a presumed low-risk or high-risk diet may be stronger in females [102]. There has been a weaker relationship between rectal cancer, more common in males, and diet with respect to colon cancer [4].

International comparison studies have shown an association between increased fat intake and CRC [103]. However, some analytical studies do not support this finding [104], particularly for rectal cancer [105, 106]. It is possible that the total amount of fat and the intake from fat as well as the specific type and origin of consumed fats play a role. Several aetiological mechanisms have been postulated to explain how saturated fat could increase the risk of CRC. The concentration of bile acids in the large bowel may be augmente by a high-fat diet. This may lead to anaerobic bacterial flora (especially some Clostridia) metabolising primary bile acids, increasing the amount of secondary bile acids, which have been linked to increased risk of CRC [107, 108]. The alkaline environment in the stool can increase the concentration of free bile acids [109].

Several studies [110, 111], but not all [112], suggest that a high intake of red meat could be associated with higher CRC risk. A number of mechanisms have been proposed regarding the contribution of meat to saturated fats intake, total caloric intake, iron intake [113], higher bile acids concentration in the bowel or exposure to nitrocompounds produced with food cooking [114]. Compounds that can accumulate in the bowel and stool include pyrrolysis products such as benzopyrene, which result from broiling or frying of meat at high temperatures and mutagenic heterocyclic amines [115]. Heterocyclic amines form in foods, especially meat, mostly with high temperature cooking, broiling, grilling, baking or pan-frying. However, a connection between meat processing, these compounds, and an increased risk of CRC is still not conclusive [116–118].

The role of fibre in determining low rates of CRCs stems from studies by Burkitt [119]. Many mechanisms have been proposed to explain the protective effect on adenoma recurrence and CRC. Fibre can act by increasing faecal bulk, speeding up transit of stools, diluting gut content, reducing the faecal con-

centration of bile acids, binding them and inhibiting their production through reduction of pH in the lumen, modifications of bacterial activity and fermentation products [119]. Studies on populations consuming diets similar in fat but differing in total fibre intake suggest a protective role for fibre [120, 121]; however, some randomised controlled trials found fibre to be useless in preventing colon cancer [122, 123]. It is still unclear if the protective effect could be due to fibre itself or to other chemicals present in high-fibre foods. Soluble fibre seems to have no protective effects, while insoluble constituents seem to be beneficial. Specific benefits of insoluble fibre have been shown for rectal cancer [124].

Some research, although not yet conclusive, supports a protective role for calcium and diets high in calcium [125]. Among the purported biological mechanisms is the ability of calcium to bind with bile acids forming insoluble soaps [126] and vitamin D related action [127].

It has been speculated that a number of foods or diet nutrients have the potential effect of CRC risk reduction. The following foods, among others, have been investigated: milk, yoghurt, olive oil, soybeans, garlic, polyphenols, flavonoids, carotenoids, selenium, vitamins A, D, C, E and specialised plant compounds like resveratrol and curcumin.

High folate diets have been associated with CRC risk reduction [128]. A factor that could increase the chances of developing CRC could be refined sugar [129], while resistant starches may prevent colon cancer [130]. Omega-3 fatty acids, present in fish oil, could correlate inversely with CRC risk [131]. Chlorinated water could increase the risk of rectal cancers [132], but the data is not conclusive [133]. Water consumption [134] and methylxanthine-containing beverages such as green tea [135] and coffee may also exert some degree of protection [136].

Energy intake, metabolism, physical activity and various measures of body size or obesity are strictly related. According to several, but not all, studies [137], regular physical activity is associated with a lower risk of CRC while a sedentary lifestyle poses a risk factor [138]. The protective effect on rectal cancer is not clear [137].

Being overweight or obese, particularly abdominal obesity [139], has been linked to an increased CRC risk, especially in men [140]. The mechanism is complex and the effect of being overweight or obese reflects the negative consequences of high energy intake and metabolic changes. Hyperinsulinaemia [141] and high levels of insulin-like growth factor-1 (IGF-1) [142] could contribute to the CRC risk. However, while being overweight and having a higher Body Mass Index may be strongly related to colon cancer, the link appears to be weaker for rectal cancer [137]. Animal studies show the benefits of reducing caloric intake alone, independently of diet composition, in preventing CRC [143, 144]. It is becoming quite evident that physical activity and appropriate energy balance can substantially decrease the risk of CRC [116], despite the fact that the association between CRC and calories is not conclusive.

There are other controllable lifestyle factors supposed to affect the risk of developing CRC. Several epidemiological research studies [145], but not all [146], have shown that alcohol consumption is associated with a moderate increase in the risk of CRC. Specifically, high alcohol intake, particularly of beer, has been implicated for both men and women in the development of rectal cancers [147, 148].

According to some studies [149], but not all [150], a positive association exists between tobacco smoking and CRC. Also, occupational exposure to some chemicals (asbestos and some organic solvents) showed an increased risk [151]. Recently, it has been suggested that cytomegalovirus infection may play a role in the development of CRC [152].

Hormonal use in postmenopausal women has been associated with a lower risk of colon cancer [153], but not clearly with rectal cancer [154]. Several studies have shown that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce the incidence of colorectal polyps and the risk of CRC [155]. The potential for the use of NSAIDs as primary prevention is under investigation, but more evidence is needed [156].

Screening for CRC

It is possible to prevent many CRCs even though we do not know the exact cause of most CRC. One of the most powerful weapons is regular screening or testing. Regular CRC screening can, in many cases, prevent the neoplasm altogether. This is because polyps can be detected and removed before they have the chance to turn into cancer. Screening can also result in finding CRC early, when the disease is highly curable.

The observation that a particular cancer has a more favourable survival rate if diagnosed at an early stage (like CRC) is important, but is only one element in the decision matrix used to determine whether or not to offer cancer screening to an asymptomatic population [157–159]. In general, the following criteria should be met [160, 161]:

1. The disease should be an important public health problem, as measured by incidence, mortality and other measures of disease burden.
2. The disease should have a detectable preclinical phase.

3. Treatment of disease detected before the onset of clinical symptoms should offer benefits compared with treatment after the onset of symptoms.
4. The screening test should meet acceptable levels of accuracy and cost.
5. The screening test and follow-up requirements should be acceptable to individuals at risk and to their healthcare providers.
6. Treatment or intervention that improves survival or quality of life (compared with not screening) should be available for patients with recognised disease.
7. Adequate staffing and facilities for recruitment, testing, diagnosis and follow-up, treatment and programme management should be available.
8. The resources allocated to the screening programme (including testing, diagnosis and treatment of patients diagnosed) should be economically balanced in relation to other healthcare priorities.

Screening measures decrease the mortality and incidence of CRC by detecting early disease (when it is highly curable) and removing precancerous lesions [162].

Research supports the benefits of screening. In 1993, the Minnesota Colon Cancer Control Study, a randomised controlled clinical trial, showed that after 13 years of follow-up, annual faecal occult blood testing (FOBT) reduced CRC mortality by at least 33%, a result that was statistically significant [163]. Subsequently, two European randomised trials, the Nottingham trial [164] and the Funen trial [165], have also found statistically significant CRC mortality reductions from biennial screening with Hemoccult.

Moreover, five case-control studies [166–170] have shown a reduction in the risk of dying from CRC using faecal occult blood screening or sigmoidoscopy. A meta-analysis of six controlled trials using Hemoccult found a 16% reduction in CRC mortality (95% confidence interval (CI) 7–23%) [171] in the populations.

after FOBT, a significant reduction has also been demonstrated, not only in mortality, but also in the incidence of CRC. The most plausible explanation is the identification and removal of the precursor lesions for CRC (adenomatous polyps) [172]. Combining FOBT with flexible sigmoidoscopy could further reduce mortality.

A sigmoidoscopy may discover many adenomas and early cancers that do not bleed and FOBT confers some added protection against proximal tumours unaccompanied by distal marker lesions discoverable at the time of a sigmoidoscopy. However, this added benefit may be quite small. Empirical studies are needed to establish and quantify any benefit and to determine if the combination is cost-effective and acceptable to patients.

Evidence for the effectiveness of the other approaches, colonoscopy and double-contrast barium enema (DCBE), is less direct and rests primarily on the studies of FOBT and sigmoidoscopy. Given the relative length of the instruments, it is not surprising that colonoscopy is more sensitive than sigmoidoscopy [173, 174]. It seems highly plausible to extrapolate the proven benefits of sigmoidoscopy to the entire colon for colonoscopy, particularly when results of the three FOBT trials are considered (studies designed on the assumption that colonoscopic screening could lower CRC mortality rates). The goal of FOBT is simply to make colonoscopic screening more efficient by identifying those most likely to benefit.

The evidence for DCBE is limited to descriptive studies showing that it has a relatively high sensitivity (50–94%) when compared with endoscopy for cancer and larger adenomatous polyps [175, 176]. Compared with FOBT, DCBE's sensitivity is much higher for adenomas and at least as high for cancer. It therefore seems plausible that screening with DCBE may also provide benefit when positive results are followed up with endoscopic polypectomy or surgery.

Although there is a general consensus concerning the efficacy of CRC screening [163–165, 173–179], there is a lack of agreement about which routine screening strategy should be adopted.

In Italy, a multicentre, randomised trial was conducted from November 1999 through June 2001 among a sample of 55–64 years olds in the general population who had an average risk of CRC, to evaluate patient compliance to different screening strategies [180]. The eligible subjects were randomly assigned to: (1) biennial FOBT (delivered by mail); (2) biennial FOBT (delivered by general practitioner or a screening facility); (3) patient's choice of FOBT or "once-only" sigmoidoscopy; (4) "once-only" sigmoidoscopy; or (5) sigmoidoscopy followed by biennial FOBT.

The participation rates for groups 1, 2, 3, 4 and 5 were 30.1% (682/2266), 28.1% (1654/5893), 27.1% (970/3579), 28.1% (1026/3650) and 28.1% (3049/10 867), respectively. Of the 2858 subjects screened by FOBT, 4.3% had a positive test result, 10 (3.5 per 1000) had CRC and 39 (1.4%) had an advanced adenoma. Among the 4466 subjects screened by sigmoidoscopy, 341 (7.6%) were referred for colonoscopy, 18 (4 per 1000) had CRC and 229 (5.1%) harboured an advanced adenoma. Segnan et al. concluded their studying saying that the participation rates were similar for sigmoidoscopy and FOBT, and, the detection rate for advanced neoplasia was three times higher following screening by sigmoidoscopy than by FOBT [180].

Perspectives on screening must concern new techniques of imaging and new analytical approaches.

Virtual Colonoscopy (CT- or MR-Colonoscopy)

Until recently, many studies on virtual colonoscopy (CT- or MR-colonoscopy) have shown different results [181–188]. The sensitivity is very low with lesions less than 1 cm and with flat lesions, while the specificity for adenoma varies from 69 to 99%.

Many technical factors could influence exam performances: bowel preparation, type of scan and the algorithm of rebuilt software. However, the lack of studies on general population, and the costs and discomfort of the technique [189] do not recommend virtual colonoscopy as a screening tool.

Normal colon cells and their DNA pass into bowel every day. Chromosomal abnormalities or DNA mutations can suggest that a colorectal polyp or cancer is present. These mutations can be detected by processing the stool. The Authors of a recent trial [190] comparing a panel of faecal DNA markers and Hemoccult II as screening tests for CRC in an average-risk, asymptomatic population conclude that the faecal DNA panel appears to be more sensitive than Hemoccult II for adenomas containing high-grade dysplasia and for the detection of early (TNM stage I, II) CRC.

Cost of Illness

In recent years, the massive economic burden of CRC has finally received increased attention. The societal benefit-cost returns on investments in CRC research and control can be evaluated through cancer economics specific studies [191]. Despite limitations that can arise in cost evaluation, the availability of information on disease costing is crucial, because it forms the basis against which cost reduction strategies and cost-effectiveness analyses can be evaluated. It is possible to determine the opportunity costs to society of CRC, by translating illness and premature death into direct, indirect [192] and psychosocial costs [193].

Two approaches have been developed to measure the cost of cancer [194]. The first one, generally known as the cost-of illness approach, tracks cost-generating events and is designed to provide an estimate of the annual aggregate, or prevalent economic impact of disease. A second approach, the incidence approach, is derived from the microeconomic field of project evaluation. It describes the longitudinal pattern of costs incurred by the average patient from the date of diagnosis as well as total lifetime costs of cancer treatment. Data based on this second approach are in demand for economic analysis. It is designed to ensure efficient use of increasingly constrained healthcare resources. Cost evaluations are influenced by many factors including: methods of cost attribution and differences in populations, treatment practices and the existing healthcare delivery patterns.

The overall economic burden of CRC is one of the highest among all neoplasms [195]. The magnitude of CRC prevalence has a significant impact on the total cost, but particularly on the indirect costs of the disease. In the United States, the total direct and indirect costs of CRC have been estimated to be around 5–6 billion dollars [196]. The total cost of CRC for France has been estimated at € 997 million [197]. Social cost structure is reported in Fig. 5. The economic burden of CRC will increase in the future as the population ages and with the adoption of more advanced and expensive diagnostic techniques and treatments.

The longitudinal economic evaluation (using incidence approach) of CRC treatment costs can be phase specific or long term. The phase-specific approach tries to associate direct costs to three post-diagnostic time periods: the initial treatment during the first three months or year following diagnosis; maintenance care or continuing care between initial and terminal treatment (non-survivors) or cessation of care (survivors); and terminal treatment during the final year or six months prior to death. The expected lifetime or total cost is subsequently derived by summing all the cumulative expected medical costs over the entire period.

The distribution of healthcare costs for CRC care is not uniform over the natural history of the disease [198]. The greatest costs are incurred during the first six months following diagnosis, which includes the

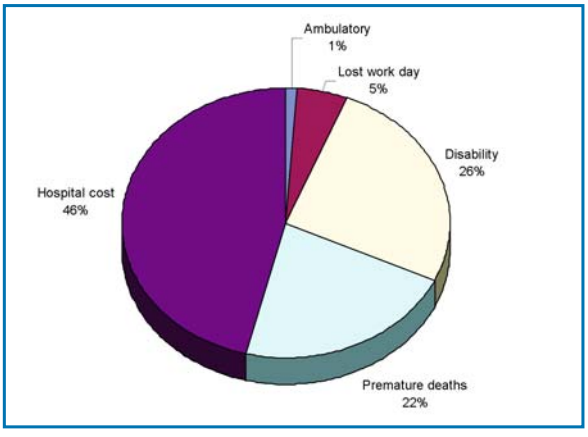

Fig. 5. Cost structure of colorectal cancer for France (1999) (Adapted from [197])

costs of disease staging, primary treatment and adjunctive therapy. The next most expensive phase is in those patients who develop recurrent disease six months prior to death. The cost profile, given by the survival function for each individual, thus has the appearance of a "U" shaped curve, with the two vertical segments of the U representing initial and terminal phase costs, and the bottom of the U as continuing care costs [198, 199]. Major costs are due to hospitalisation [200], surgery and chemotherapy [201], which can be relatively cost-effective [202, 203]. Additional costs include: drugs, physician office visits, and the costs for home healthcare, hospice care and skilled nursing facilities care. Hospitalisation has been suggested to represent 65% and 61% of the lifetime cost of care delivery in colon and rectal cancer respectively [204].

There is not a monotonic relationship between stage and long-term cost. The costs of treating very early and very late stage cancers seem significantly lower than those of treating cancers in the intermediate stages. Costs are relatively high for stage II and III and lower for *in situ*, stage I and IV CRC [198]. A screening programme that shifts cases towards earlier stages of diagnosis may produce substantial savings in terms of lower treatment costs. For CRC, initial care and total cancer related costs do not seem to vary according to gender. However, costs do appear to increase in the presence of comorbidities [198] and for younger patients [205]. Costs seem to be somewhat higher for cancer of the rectum compared with cancer of the colon [198, 206]. This difference has been related to an increased use of new and expensive chemotherapy for the more advanced stages as well as the use of radiotherapy, which can be cost-effective [207], for stages II and III rectal cancer [204].

Several studies in North America and Europe addressed treatment cost issues of CRC [208–210]. Initial care costs have been estimated between US $18 000 and $ 22 500 [205, 211–213] and continuous care costs between US $1300 and $1500 per year [205, 213]. Costs are higher on an annual basis among persons with later stages of cancer and shorter survival time [213]. Terminal phase costs have been estimated between US $12 000 and $15 000 [205, 213]. In Canada, the average treatment cost per case for all stages of colon and rectal cancer was estimated to be CAD $ 29 110 and $34 475 respectively [204]. In this research, the average lifetime cost of managing patients with CRC ranged from CAD $20 319 per case for TNM stage I colon cancer to CAD $39 182 per case for stage III rectal cancer. Fig. 6 shows rectal cancer costs.

Research has shown that relatively high and non-uniform frequency of hospital admissions are associated with CRC [214, 215]. Hospitalisation may be more relevant in patients with advanced disease and worst prognosis [216]. Extensive variation has been reported worldwide in resource utilisation among centres and, thus, costs [217–219]. The study of appropriateness in care settings and resource utilisation patterns may lead to better quality and cost-saving strategies. It is important to stress that higher costs do not necessarily mean higher quality of care.

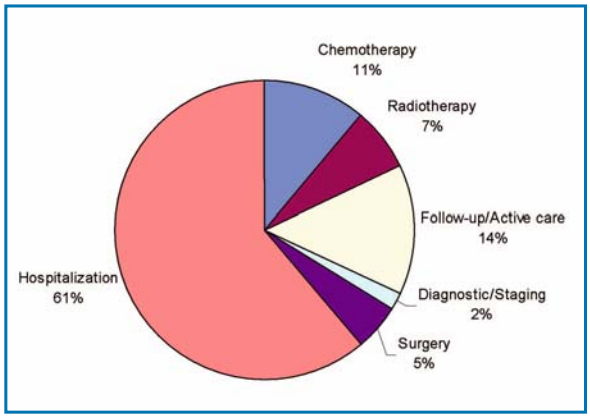

Fig. 6. Distribution of per patient lifetime costs of rectal cancer by intervention – all stages (Adapted from [204])

Cost of Screening Strategies

CRC is an expensive disease to treat and by preventing its development, the avoided costs of treatment can be offset against the costs of a screening programme [220]. The cost of population-based screening in public funded healthcare systems is an issue of compelling priority. It is required for screening programmes in order to support appropriate decision-making. Costs of a screening programme include: direct costs, time costs (patients' lost time while receiving screening) and productivity costs (patients' lost productivity). Estimating direct screening costs involves the identification and measurement of the inputs (and their values) that go into performing the specific tasks of screening, and required diagnostic evaluations and treatments. Other factors that contribute to the total cost of secondary prevention programmes are: relevant programme structure and organisation, population compliance, chosen screening schedule and unit costs of screening. The most useful ways to express the opportunity cost of screening are "cost per unit of effectiveness" or "cost per unit of benefit". A widely applied economic evaluation is cost-effectiveness.

A screening is regarded as cost-effective when the

incremental cost of obtaining a unit of health effect from screening is compared with no screening below an accepted benchmark. According to international literature, the benchmark value commonly applied to preventive technologies is roughly US $40 000 per added year of life [221]. Furthermore, a screening strategy is considered efficient if there is no alternative that results in more life years gained with equal or less cost. Economic evaluation has regarded screening by FOBT [222, 223], DCBE [175], flexible sigmoidoscopy [224, 225] and colonoscopy [174, 226]. Results of different cost-effectiveness analysis vary consistently among different models and scenarios.

Screening strategies for CRC seem to be cost-effective compared with no screening [227, 228]. CRC screening compares favourably to other cancer screening strategies (cervical cancer screening and mammographic screening) [229] or other life-saving treatments such as kidney dialysis or coronary artery bypass surgery [230]. Colorectal screening may have an average cost-effectiveness ratio between US $10 000 and $30 000 per year of life saved, thus below the US $40 000 threshold [231]. From an economic point of view, results indicate that CRC screening should be warranted for the average-risk adult over the age of 50 years until the age of 80 years [221].

Each alternative can be cost-effective, but it is not easy to indicate which screening approach has the best cost-effectiveness ratio from the societal perspective [231] because each approach is strongly influenced by unit cost of the exam [225] and screening schedule [232].

It has been reported that a flexible sigmoidoscopy performed every 5 years and an annual FOBT are the two most cost-effective screening strategies [229, 233, 234]. However, according to other studies, a colonoscopy every 10 years could be the best cost-effective screening strategy [226, 235, 236].

A screening strategy is cost-saving when it results in a net economic saving as well as a saving in years of life [220]. Screening-induced savings are mainly due to the prevention of cancer and therefore represent savings on cancer treatment. According to the literature, flexible sigmoidoscopy CRC screening may result, for a 30 years screening programme, after 35 years, in a net savings of direct healthcare costs [220].

Decisions about whether to make population screening investments appropriately depend on a variety of factors, some related to and others external to the economic evaluation evidence. All in all, the economic implications of colorectal screening for future research and policymaking are clear: CRC screening in average-risk adults is a good long-term investment for society.

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Diagnostic Imaging: Diagnosis and Staging

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Rectal Anatomy

The analysis of the anatomy of the distal portion of the large intestine and of the sigmoid colon at the level of the third sacral vertebra is continuous with the distal portion of the large intestine: the rectum.

The longitudinal musculature that at the colonic level is arranged in three bands, the *taeniae*, at the colorectal junction expands again to form a continuous layer of longitudinal musculature [1]. The *haustra* disappear and the distal portion of the intestine appears as a smooth, almost cylindrical tube. The regular mucosal folds are missing, however the rectum may show some folds (Fig. 1). One of these is usually located 8–10 cm above the anum (Kohlrausch fold) and below it the rectal lumen dilates to form the rectal ampulla. The rectum approaches the anterior surface of the posterior pelvic wall and has a peritoneal covering extending on to its lateral and anterior surface and reflecting onto adjacent organs below the Kohlrausch fold (Fig. 1). In women the peritoneal recto-uterine reflection forms the pouch of Douglas; in men the peritoneal reflection between the rectum and prostate is obliterated and forms Denonvilliers fascia. A thin rectovaginal septum separates the rectum from the vagina. The rectum is about 12–15 cm long and is divided into three portions: upper, middle and lower. The upper rectum extends from the recto-sigmoid junction (readily recognised by the surgeon because the *taeniae* have disappeared, but lacking a precise radiologic reference) to the middle rectal valve (Kohlrausch valve) located on the right lateral margin of the ampulla at the level of the peritoneal reflection. Thus, the upper rectum is intraperitoneal [2]. The mid and lower rectum are extraperitoneal. On the left lateral margin two valves may be present (Houston's valves). The lower valve represents the superior limit of the lower rectum while the superior limit of the mid-rectum is Kohlrausch valve (Fig. 1).

The anal canal is 3–4 cm long and is located between the rectum superiorly and the perianal skin inferiorly [3]. Its superior limit is defined by the internal anal sphincter and by the ano-rectal angle, delimited by the *levator ani* muscle, while for anatomists the ano-rectal junction corresponds to the pectinate line following the level of the anal valves [4].

The pelvic cavity is grossly cone-shaped and the muscle and bone segments constitute the walls and the pelvic floor [5]. Anteriorly the walls are represented by the pubis and laterally by the internal obturator muscles, posteriorly by the sacrum and the pyramidal muscles.

The internal obturator muscle originates from the pubis and the obturator membrane, reaches the lesser ischiatic foramen to leave the pelvic cavity and insert onto the greater trochanter. The pelvic floor is exclusively muscular, it supports the intrapelvic viscera and has the shape of a roof. The steepest point corresponds to the anal orifice. The pelvic floor essentially consists of the levator ani, extending from the horizontal portion of pubis lateral to the aponeurosis of internal obturator muscles. Between the anteromedian fibres of these muscles there is a triangular gap covered with the urogenital diaphragm through which the urethra and the vagina pass into the perineum. Posterior to the urogenital diaphragm, the fibres of *levator ani* muscle cross, delimiting the anal orifice, and reach the sacrococcygeal raphe.

The levator ani muscle is oblique to reach the steepest point of the floor, thus transverse CT scans section it almost perpendicularly. Only coronal MR scans visualise the muscle completely [6]. Posteriorly, the pelvic floor is composed of the ilio-coccygeus muscle continuous with the levator ani. Outside the 'pelvic cone', posteriorly, the posterior group muscles (greatest, middle and least gluteal muscle) transversally located between the sacrum, the wing of ilium and the femur, attach the lower limb to the pelvis together with the muscles of the anterolateral group of the leg extending longitudinally between the iliac spine and proximal femur. Outside the pelvic cone there are the pectinate and external obturator muscles transversally located between the pubis and the posterior aspect of femur.

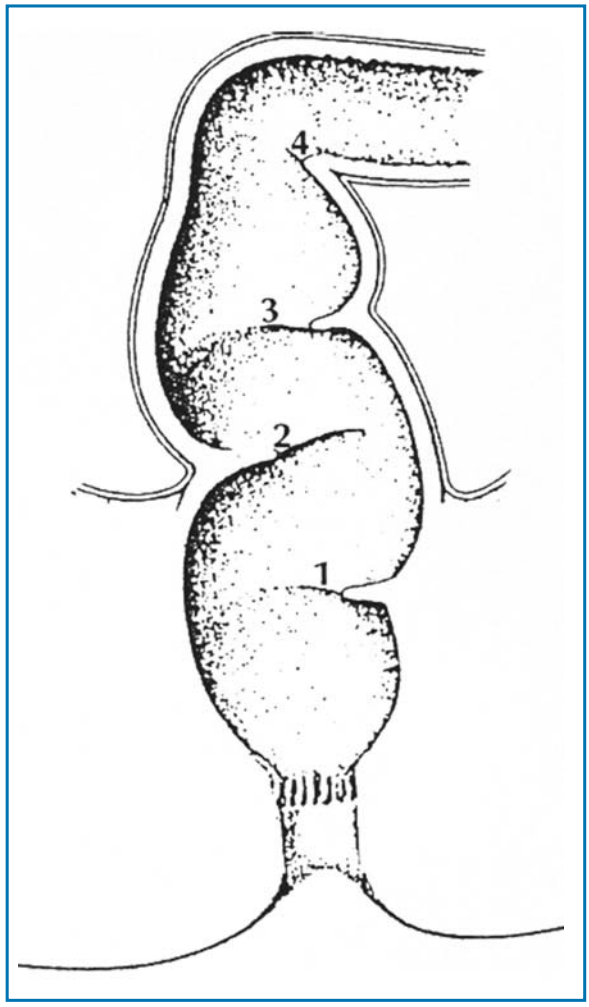

Fig. 1. Anatomy of the rectum: scheme. At about 8–10 cm from internal anal sphincter, on the right lateral wall there is a Kohlrausch valve (*2*) corresponding to the peritoneal fold. It represents the upper limit of mid-rectum. On the left lateral wall there are the inferior (*1*) and superior (*3*) Houston valves. Inferior Houston valve (*1*) represents the upper limit of the lower rectum while the recto-sigmoid junction (*4*) is not definitely recognised on imaging. It is located 10 cm from the anus

Diagnosis of Colorectal Cancer: Colorectal Enema

There are two ways to study the mucosal side of colon: radiology and endoscopy. These methods are usually thought to be antithetical, while they are actually complementary.

The introduction of the double contrast methods has corresponded to the advent and the technological advance in endoscopy. The diagnosis of rectal cancer can be supported by radiology as well as by endoscopy. They are two excellent methods for diagnosis and the choice of either of them is related to the existing social setting and health service standard.

The elective radiologic procedure for the study of colon and rectum is the double contrast enema based on the instillation of a barium sulphate suspension and of its evacuation followed by inflation of air with double contrast examination of the colon. Drug-induced hypotonia is necessary to suspend peristalsis. Intestinal preparation for perfect colonic cleansing is a fundamental prerequisite, its inadequacy being one of the major causes of non-diagnostic exams [7]. The superiority of double contrast enema as compared to the single contrast enema is now well established [8].

Indications for the procedure are the same as those mentioned for colonoscopy. The only surgical indications are in the neonatal period (intussusceptions).

In cases of acute colonic bleeding, the first choice exam is definitely endoscopy. It should always be performed with double contrast enema with pharmacologic hypotonia except for the following cases: elderly or non-complying patients, post-operative controls (water-soluble contrast medium) and pseudo-obstructions.

Technical limitations are mainly due to faecal residues or artefacts (flocculation of barium, gas bullae) which may mimic inflammation, ulceration or polyps. Absolute contraindications for enema are: pregnancy; toxic megacolon; suspected colonic perforation; immediately preceding endoscopic exam, especially if with biopsy; acute diverticulitis or peritonitis; acute colonic obstruction; peritoneal fistulae, anatomical malformations (malrotation, hernia); and ischaemic colitis.

As for the rectum, it can be stated that it is the portion of the entire colon most readily examined by radiology [9]. In a report from the literature [10] 15% of the lesions were missed by rectal exploration and rectoscopy and were detected on doing an enema. However it can be stated that both exams miss some lesions and that in the rectum the two methods show a similar sensitivity in the identification of neoplasms [11, 12]. In our opinion, rectal enema is fundamental in a patient with rectal cancer, especially if pre-operative radiosurgical therapies requiring the exact intra- or extraperitoneal location of the tumour are planned.

Signs and Findings

The macroscopic forms of rectal cancer are in agreement with the endoscopic findings:

– polypoid or vegetating forms tend to grow into

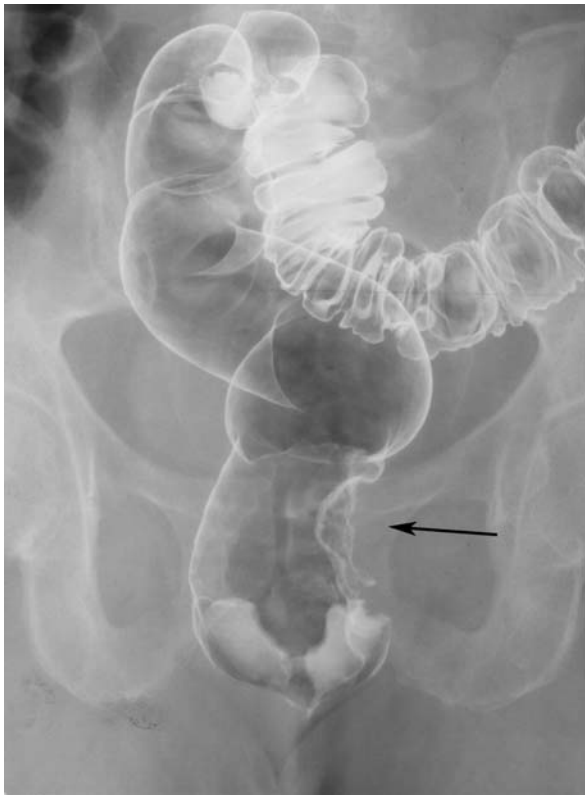

Fig. 2. Double-contrast barium enema. AP view. Flat vegetating lesion with wide, irregular and retracted base: adenocarcinoma of the lower rectum (*arrow*)

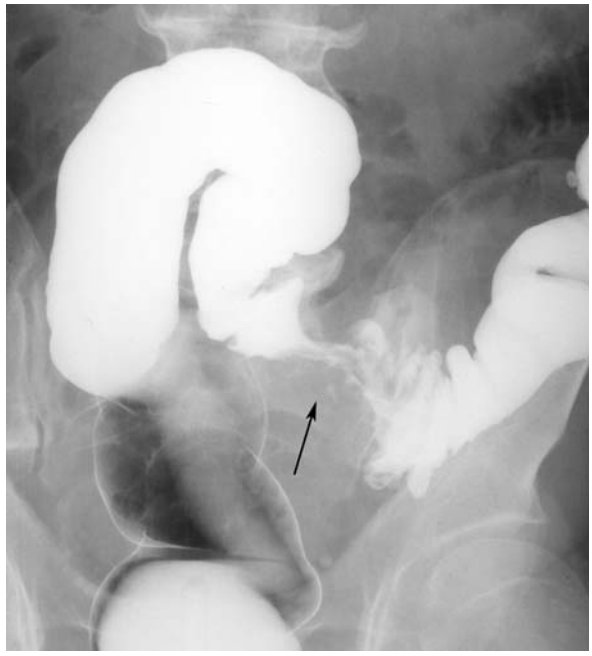

Fig. 3. Double-contrast barium enema. AP view. Rectal tumour with circumferential growth in the sigmoid colon (*arrow*), with severe stenosis of the colonic lumen

and to obstruct the intestinal lumen showing an irregular ulcerated surface, irregular, rigid and retracted base from mural infiltration;
- infiltrating forms starting as plaque lesions growing on the visceral walls. If the growth is circumferential the tumour is annular or has the appearance of the core of an apple (Fig. 2);
- stenosing forms with more or less marked reduction of the intestinal lumen (Fig. 3).

Frequently several macroscopic aspects are combined together.

The strong points of barium enema are represented by: (1) concomitant visualisation of the viscus in its entire length (pan vision); (2) stenotic portions are not an obstacle; (3) the function is studied; (4) radiographs enable an objective documentation of the lesions. The weak points are: (1) the need for a high standard procedure; (2) the need for perfect intestinal cleansing; and (3) the need for complying patients.

An extremely rare reaction from barium hypersensitivity has been reported [13]. The most severe complication is definitely perforation, which in most cases involves the rectum and is related to the air inflation, especially when performed with balloon catheters in a diseased rectum. Colonic enema should never be performed after perendoscopic biopsy in a diseased or normal colon, as this is the major predisposing factor for mural perforation [14].

Minor complications may be considered as the pain from gas distension or following the exam.

Colonoscopy and double contrast colonic enema have an overall accuracy of about 90%.

Staging Rectal Cancer

Colonic Enema

For the clinical staging of the tumour, necessary for correct planning of the therapeutic approach, the information supplied by the two methods are: the macroscopic appearance of the tumour; its size; its occlusive character; its distance from the anus and exact location (intra- or extraperitoneal).

As for the first, the main forms have already been

described. The evaluation of the size plays a major role, particularly with the introduction of protocols of combined and neoadjuvant therapies which necessitate a precise definition. In fact, for a correct assessment of the effects of radiation and/or chemotherapy, the size of primary tumour is required for pre- and post-treatment comparison.

For this purpose, the longitudinal length of the tumour as well as the circumferential involvement, expressed as quarters of circumference, should be defined.

Finally, the diagnostic findings should supply information on the degree of stenosis (expressed as per cent of residual lumen) caused by the tumour and on the short-term risk of intestinal occlusion. These data may be used for the indication for preventive diverting colostomy, when the features of the tumour, after complete staging, suggest pre-operative neoadjuvant treatment.

Similarly important in the planning of surgery is the assessment of the distance from the anal sphincter. For uniform criteria of assessment and for useful information for the surgeon who must decide on the type of surgery, we believe that the most important parameter is the distance between the inferior margin of the tumour and the internal anal orifice. This represents exactly the rectal length that can be used for a conservative operation of the sphincter, excluding the length of the anal canal, which varies from case to case and does not represent a useful segment for intestinal anastomosis. Differential criteria for the diagnosis of intra- or extraperitoneal location are also very important to plan pre-operative treatment. A comparison of double contrast radiology *vs.* rectoscopy was carried out in 23 patients with rectal cancer based on the above-described parameters.

In 7 patients (30%) the assessment of the length of tumour was impossible because of the obstacle represented by the neoplastic stenosis across which the endoscope could not be passed. Fifty per cent of these cases were shown to have a circumferential involvement on double-contrast enema and in the other 50% 2/4 of the circumference were involved. Most likely the vegetating component of the tumour hindered the advancement of the instrument. In 16 patients (70%) comparison of results was as follows: in 9 patients (56%) they were concordant; in 7 patients (47%) there was a difference of 1–2 cm and endoscopy tended to indicate a shorter length as compared to the enema.

The assessment of the circumferential involvement of the rectal lumen by the tumour is expressed in quarters of circumference: 18 patients (78%) showed concordant results while discordant results were observed in 5 patients (22%). Rectoscopy in discordant cases assessed 1/4 more than the enema. In the 9 patients with 4/4 circumferential involvement the two methods were fully concordant.

As for the important parameter of the distance of tumour from the internal anal sphincter in the 23 patients under study, in 6 (26.7%) the results were concordant while in 8 patients (34.7%) the results were discordant by only 1 cm. In 9 patients (39.1%) the results were discordant by 2–3 cm and in most cases the tumour was located in the mid-rectum. Rectoscopy tended to exceed the measurement by the enema.

Computed Tomography

The pre-operative diagnosis and staging of rectal carcinoma represent in our country a problem of much social concern, considering the high incidence of mortality for this neoplasm (about 4 000 deaths/year in Italy) [15].

In recent years, the advances in surgical procedures and pre-, intra- and post-operative radiotherapy have enhanced the percentage of operability, while the risk of post-operative recurrence and the incidence of distant metastases are constant: this is partly due to the inadequacy of pre-operative staging. In fact the risk of recurrence is substantially related to two factors: (1) the extent of rectal wall infiltration; and (2) the presence of metastatic lymphadenopathy [15, 16]. These occurrences should be known to the clinician in order to plan the correct pre-operative adjuvant radiotherapy and, if necessary, to change the surgical approach. A correct pre-operative assessment of rectal carcinoma is thus necessary, taking into account the clinical evaluations (rectal exploration, rectoscopy, biopsy) and the use of combined diagnostic imaging (double contrast enema, transrectal sonography, computed tomography and magnetic resonance), where each procedure plays its own role in the identification and staging of the tumour [17].

The criteria used to define the stage of rectal carcinoma have been established by the NIH Consensus Conference of 1990, which indicates the EMU as the reference system of staging. The TNM classification has been used throughout this study (Table 1).

The present indications for computed tomography (CT) in rectal cancer are: the site of tumour, its infiltration in the perirectal fat or in the adjacent organs, the nodal spread and distant metastasis.

Table 1. TNM classification of rectal tumours

	TNM			Dukes
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	A
Stage II	T3	N0	M0	B
Stage III	Any T	N1	M0	C
	Any T	N2–3	M0	C
Stage IV	Any T	Any N	M1	

Computed Tomography: Signs and Findings

T Staging

Primary rectal tumours on CT may appear as: intraluminal focal mass; plaque thickening of the viscus involving one or several quarters of its circumference, associated with an intraluminal component.

It should be considered that the normal thickness of the rectal wall is less than or equal to 3 mm [18]. The finding of focal or diffuse thickening should definitely indicate a neoplastic disease when the wall is over 5–6 mm thick [19, 20]. However most lesions, on examination, are over 2 cm [18].

The CT density of the neoplastic tissue is about 40–60 HU, usually hypodense as compared to the normal wall and to date there have been no definite findings to relate the densitometric values of the lesions with the various histologic types. It has been observed that the finding of calcifications within the lesion suggest the diagnosis of adenomucinous carcinoma [18, 19].

In our personal experience we have noted that mucinous carcinoma, which is relatively infrequent, on CT has an inhomogenous appearance with typical areas of hypodensity related to the high extracellular contents of mucin, alternating with solid tissue characterised by contrast enhancement. Potentially malignant villous adenoma when bulky is shown as an intraluminal mass with homogenous water-like density interfaced with a branching appearance of the remaining portions.

Because CT does not recognise the 5 layers of the rectal wall (contrary to transrectal sonography and MR imaging), it is not able to differentiate the neoplasm limited to the mucosa (T1) to that involving the muscolaris (T2). It has now been definitely established that the more specific role of CT is to differentiate the advanced stages of the disease (T3–T4): the extent of involvement of pararectal fat and of adjacent organs, adenopathy and metastasis are recognised. It is in fact well known that the diagnostic accuracy of CT is proportional to the stage.

The infiltration of the perirectal space, namely the advance from stage T2 to stage T3, can be detected on CT (77% sensitivity, 64% specificity, 73% accuracy) based on the identification of irregular external margin at the level of neoplasm with an 'indented' profile and hyperdense strands in the perirectal fat originating from the neoplasm (Figs. 4 and 5).

This is undoubtedly one of the more delicate phases of staging: extremely thin strands of neoplastic tis-

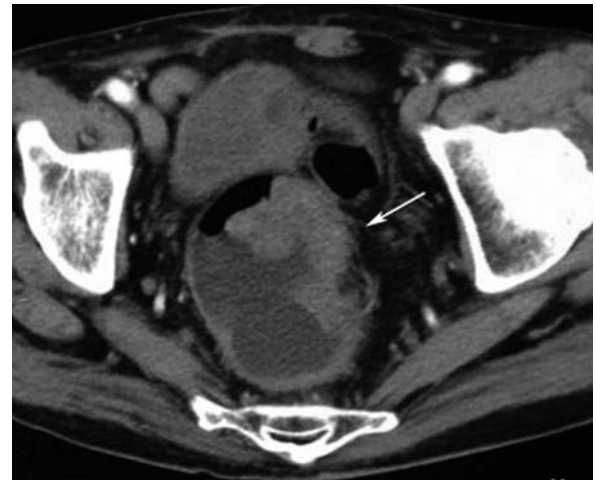

Fig. 4. Contrast-enhanced CT: T. Adenocarcinoma of the left lateral wall of the rectum, with irregular interface with the perirectal fat (stage T3)

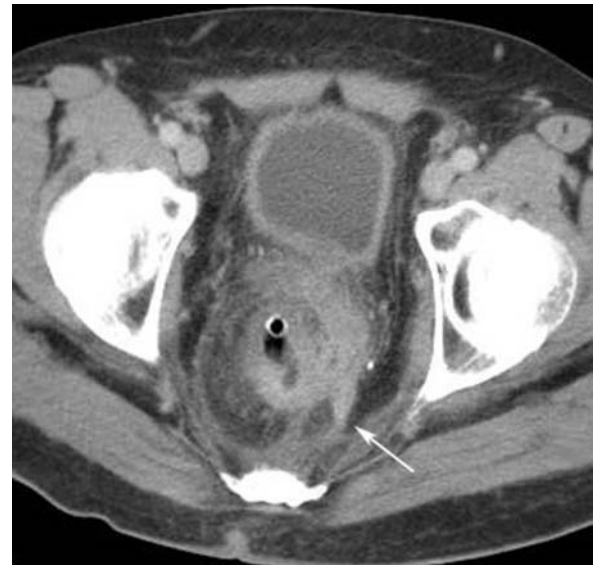

Fig. 5. Contrast-enhanced CT: T. Adenocarcinoma of the left lateral wall of the rectum with hyperdense strands infiltrating the perirectal fat up to the perirectal fascia that appears thickened (*arrow*)

sue beyond the wall must be recognised or the extent of disease should be suspected even in the presence of minimal densitometric alterations of the perirectal fat [21–27]. The ability to visualise the infiltration of contiguous adipose planes is an important parameter for diagnosis as well as for therapy, as pre- or intraoperative radiotherapy may be hypothesised [17]. However, it should be kept in mind that also peritumoral lymphangitis, vascular ectasia adjacent to the wall or perirectal inflammation may be responsible for CT hyperdensity of the perirectal fat or of strands mimicking a stage T3 disease [15, 19, 20, 28] (Fig. 5).

In the assessment of tumour infiltration in the perirectal fat, it is important to distinguish the involvement of the perirectal fascia. This condition represents the first sign of the advance from stage T3 to stage T4. The fat tissue adjacent to the external rectal surface is covered with the perirectal fascia to form the adipose rectal capsule. The perirectal fascia is normally recognised on CT. In the presence of inflammatory or neoplastic processes it thickens at times asymmetrically and its identification is even easier [18, 22] (Figs. 4 and 5).

CT plays a major role in the definition of stage T4 (100% sensitivity, 92% specificity, 93% accuracy), namely in the identification of signs of infiltration of the anatomical structures and of adjacent pelvic organs (perirectal fascia, seminal vesicles, uterus/vagina, prostate, pelvic muscles, bone segments, etc.) [17, 20, 21, 24]. Two major CT signs indicate a direct involvement of pelvic organs: (1) the loss of adipose cleavage planes between the neoplasm and the adjacent organ. However it should be underlined that the obliteration of the adipose plane may be due also to lymphatic or vascular problems, or cachexia, with no real infiltration [18]. In some cases, the excessive gas distension may be *per se* the cause of the loss of cleavage with adjacent structures [19, 27]. (2) The finding of direct infiltration by the tumour or the observation of a 'bridge' to the tumour and the adjacent organ with densitometric features similar to those of the rectal tumour.

It is questionable whether the simple thickening of the perirectal fascia should be considered a sign of disease spread [22, 24].

From reports in the literature concerning series of rectal tumour staging, the most frequently involved organs are bladder and prostate followed by the seminal vesicles, ureters, vagina, uterus, ovaries and small intestine [18, 19].

The involvement of the bladder is readily established based also on the presence of air within it due to the formation of fistulous tracts. The finding of hydronephrosis is suggestive of ureteral infiltration [18, 19].

It should be stressed that sometimes it is difficult to distinguish a primary rectal tumour from one originating in the prostate, uterus or ovary, secondarily involving the rectum [19, 28].

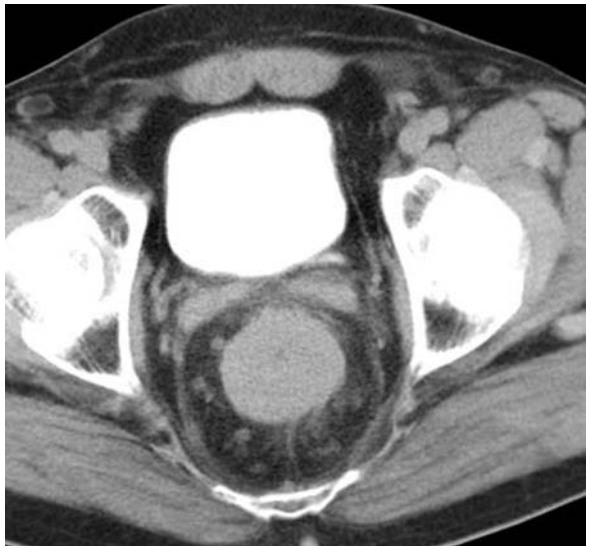

Fig. 6. Contrast-enhanced CT: N. Multiple (>3) lymph nodes in the perirectal fat

On CT, definite involvement of muscular structures (*levator ani*, internal obturator, coccygeal, piriform and greatest gluteal muscles) is defined based on the detection of enlargement of the involved muscle. It should be noted that because of the normal lack of adipose planes between the *levator ani*, the most caudal portion of the rectum and the anal sphincter, in this site the assessment of the extramural infiltration is frequently impossible [18].

Direct infiltration of adjacent bone structures (the sacrum and coccyx) can be diagnosed based on the finding of neoplastic tissue adjacent to gross areas of bone destruction. In other cases, the finding is not so clear and only the use of suitable windows for the study of the bone can evidence a minimum infiltration with areas of osteolysis limited to the cortex [18].

N Staging

Nodal involvement can be locoregional or distant. The first lymph nodes to be involved by the tumour are perirectal lymph nodes. N1 indicates the presence of 1–3 pathologic perirectal lymph nodes, and N2 the presence of over 3 lymph nodes present in the same site (Fig. 6). Perirectal lymph nodes run along a central route that along the superior haemorrhoidal artery reaches the inferior mesenteric artery (IMA) to its opening into the abdominal aorta. Involvement of

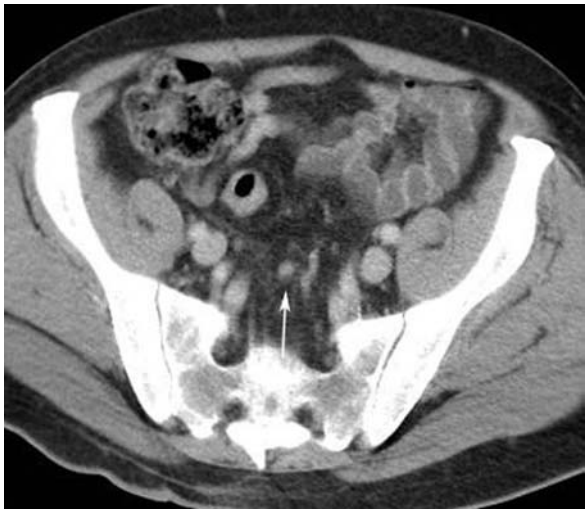

Fig. 7. Contrast-enhanced CT: N. Lymph node along the inferior mesenteric vein (*arrow*)

IMA lymph nodes defines N3 (Fig. 7). Lateral outflow lymph nodes localised in the ischiorectal fossae through the inferior haemorrhoidal and pudenda reach the internal iliac chain. This is the usual route of neoplasms of the anal canal through which rectal tumours spread only in the presence of a lymphatic central obstruction. Involvement of lateral lymph nodes defines M1.

Nodal spread of metastases is detected on CT (74% sensitivity, 66% specificity, 71% accuracy) according to the criterion of the size: in the past only lymph nodes of over 1 cm in diameter were considered positive. In some cases, this finding resulted in understaging, thus with major prognostic and therapeutic failures [15, 17, 20, 22, 25].

It is well known that the size of lymph nodes may have no relation to the neoplastic involvement, as proven by the frequent histologic finding of metastatic foci in lymph nodes of 1 cm or less in diameter [15, 17, 18, 20, 29].

However it should be underlined that CT does not always enable the differentiation of inflammatory and metastatic lymphadenopathy, because the densitometric pattern is almost identical. This could result in diagnostic failure and overstaging. Together with other Authors [15, 20] we consider pathological lymph nodes visualised at the perirectal level apart from their size while the latter is taken into account for iliac, mesenteric, inguinal and para-aortic lymph nodes. In our opinion the use of contrast helps in the differentiation of small vascular structures from lymph nodes.

M Staging

M1 defines the presence of lymphadenopathy outside the central route of outflow and in the para-aortic site and the presence of distant metastasis. CT plays a major role also in M staging. In about 15% of cases rectal carcinoma shows on first diagnosis secondary liver localisation [18]. It has a satisfactory sensitivity in the detection of hepatic metastatic lesions; in no contrast scans metastases appear as hypodense area. In sporadic cases these lesions may present small calcifications, typical of mucinous adenocarcinoma [19]. In dynamic scanning (contrast bolus) in the arterial phase metastases show ring enhancement. In the late phase (10–15 min after bolus) the lesions tend to become hypodense with the adjacent parenchyma.

There is central enhancement in case of a central fibrotic or necrotic focus.

The detection of small metastatic hepatic lesions at surgery for rectal carcinoma is important because they may be resectable with consequent improvement of the patient's survival.

Adrenal metastases have also been observed in patients with rectal cancer. The findings of enlarged inhomogeneous or asymmetrical adrenal glands should be suggestive of secondary location [19]. The finding of ascitic effusion into the peritoneal cavity is a sign of peritoneal metastatic spread [4].

Magnetic Resonance Imaging

The successful introduction of magnetic resonance imaging (MRI) for pelvic diseases has, in recent years, led to the gradual replacement of CT by MRI for local and regional rectal cancer staging. Initial MR studies were performed with a body coil. Because conventional body coil techniques showed a resolution that was still insufficient to differentiate the individual layers of the rectal wall, overall accuracies reported for MRI with a body coil have not been any better than those reported for CT, with values ranging from 59 to 88% [15, 30–35].

The introduction of endoluminal coils facilitated improved image resolution and made detailed evaluation of the layers of the rectal wall feasible. This was also reflected in improved and more consistent T staging, with accuracy ranging between 71 and 91% [36–43]. Endorectal MRI can be as accurate as endorectal US for staging of superficial tumours, as shown in studies comparing the two endoluminal techniques [36, 37]. However, some problems remain with endorectal MRI. Besides the limited availability and high cost, MRI with an endoluminal coil, especially when used in isolation, has a limited field of

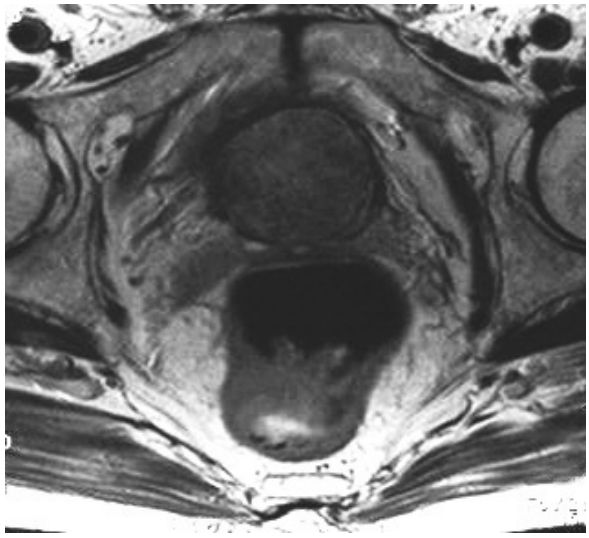

Fig. 8. Magnetic resonance imaging. Axial T1-weighted spin echo image shows a moderately hyperintense lesion in the rectum with sharp interface with the peri-rectal fat (stage T2)

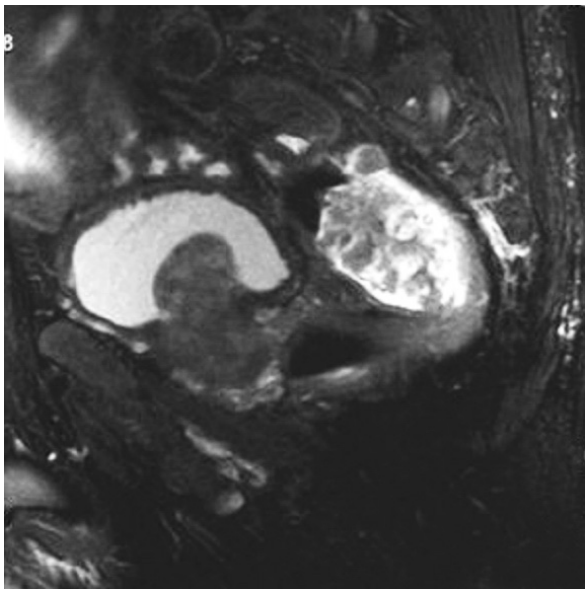

Fig. 9. Magnetic resonance imaging. Sagittal fat sat T2-weighted turbo spin echo image shows a hyperintense lesion in the middle rectum

view. Like endorectal US, the mesorectal fascia and surrounding pelvic structures are difficult to visualise owing to the sudden signal drop-off at a short distance from the coil [44]. Furthermore, the positioning of an endoluminal device can be difficult or impossible in patients with high and/or stenosing tumours, and failed insertion rates of as high as 40% have been reported in patients with rectal cancer [45].

With the introduction of dedicated external coils, especially phased-array coils, improvement in MRI performance was expected [46–50]. The advantages of high spatial resolution with a large field of view make phased-array MRI suitable for staging of both superficial and advanced rectal tumours (Figs. 8 and 9). However, Authors of the first studies that used MR with the multiple surface coil technique reported an overall accuracy for T staging of only 55–65% and showed no benefit compared with the use of a body coil or even with CT [51, 52]. The low performance of MRI in these studies could have been attributed to the low spatial resolution that was used with the early phased-array techniques. But even when a higher spatial resolution was applied with the new generation of phased-array coils, the accuracy for T staging was not as high as anticipated, with values varying between 65% and 86% [50, 51], and was not as reproducible as expected, with considerable interobserver variability [53]. One exception to the above was the study by Brown et al. [49], who reported 100% accuracy and complete agreement between two readers on the prediction of tumour stage with phased-array MRI results.

Most staging failures with MRI occur in the differentiation of T2-stage and borderline T3-stage lesions, with overstaging as the main cause of errors. Overstaging is often caused by desmoplastic reactions [43, 49, 53], and it is difficult to distinguish on MR images between spiculation in the perirectal fat caused by fibrosis alone (stage pT2) and spiculation caused by fibrosis that contains tumour cells (stage pT3) [53].

The present T-staging system is sometimes used for clinical decision making. Post-operative combined chemotherapy and radiation therapy has been the standard in the United States for patients with T3- and/or N1-stage tumours. There is now a growing tendency to give the adjuvant therapy pre-operatively and, therefore, a need for a good imaging method to select patients at high risk. In this respect, the present T-staging system does have its shortcomings: it does not discriminate between tumours with a wide circumferential resection margin (CRM) and tumours with a close or involved CRM. Although most of these tumours are classified as stage T3, they have a different risk for local recurrence. It has been repeatedly shown that the distance from the tumour to the circumferential mesorectal resection plane is a more powerful predictor for the local recurrence rate than is the T stage [54, 55]. It is therefore probably more important to use imaging to identify those tumours that will have a close or involved resection

margin so that they can be selected for more extensive (neoadjuvant) treatment.

Rectal cancer has two main routes of lymphatic spread. For the upper portion of the rectum, the route is upward along the superior rectal vessels to the inferior mesenteric vessels. The lower portion of the rectum shows an additional lateral lymphatic route along the middle rectal vessels to the internal iliac vessels. Downward spread along the inferior rectal vessels to the groin is unusual except in very advanced cases and when the anal canal is involved.

Results of early anatomic studies [56–60] showed that over half of the metastatic nodes were within 3 cm of the primary tumour and were smaller than 5 mm in size. With standard total mesorectal excision (TME), the perirectal nodes are removed with the primary tumour but the internal iliac nodes are left *in situ*. In lower rectal cancer, therefore, there is a risk that involved internal iliac nodes will be left behind, with the chance for local recurrence. The magnitude of this risk was illustrated by Moriya et al. [61], who showed that as many as 28% of lymph node-positive distal rectal cancers have involvement of lateral nodes, and in 6% of cases those lateral nodes were the only lymph nodes involved. This means that disease in 6% of patients is incorrectly staged as node-negative at TME. The fact that nodal disease is a prognostic indicator not only for distant metastases but also for local recurrence has been confirmed in the large Dutch TME trial [62], where patients with stage III (TxN1) disease had a 10-fold higher risk for local recurrence than did those with stage I (T1–2N0 stage) disease and a threefold higher risk than did those with stage II (T3N0 stage) disease.

When the treatment strategy is post-operative chemotherapy and radiation therapy for patients with T3N1 disease, there is little need to identify the lymph node status pre-operatively. When the emphasis is on pre-operative radiation therapy, with or without chemotherapy, and one wants to select patients at high risk, determination of lymph node status becomes essential.

Some surgeons, mainly from Japan, claim improved local control by adding extended pelvic lymphadenectomy to resection of the rectum. This approach is not favoured by most surgeons because of the additional urologic and sexual morbidity, while the benefit is unclear. Again, selection of those patients with the highest risk for lateral lymph node metastases could be useful for centres where pelvic lymphadenectomy is practised.

Identification of nodal disease is still a diagnostic problem for the radiologist. Despite the identification of lymph nodes as small as 2–3 mm on high-spatial-resolution images, reliable detection of nodal metastases is presently not possible. The radiologic assessment of nodal involvement generally relies on morphologic criteria such as the size and shape of the node [63–65]. The problem with morphologic imaging, however, is that with enlarged nodes it is difficult to distinguish between reactive and metastatic nodes, and with small nodes micrometastases are easily missed. An additional problem in rectal cancer, as compared with other pelvic tumours, is the high frequency of micrometastases in normal-sized nodes. Large variations in accuracy (62–83%) for nodal detection can be found for endorectal US [67, 68], as well as for CT (22–73%) [29, 68, 69]. Despite the superior soft-tissue contrast, it has not been possible with unenhanced MRI to accurately distinguish between inflammatory and metastatic nodes on the basis of signal intensity criteria, nor has the use of non-specific MR contrast agents improved detection accuracy. Accuracy rates for nodal detection with unenhanced MR imaging vary between 39 and 95% [70–72].

An alternative method would be metabolic imaging by fluorodeoxyglucose positron emission tomography (PET). Fluorodeoxyglucose PET scanning has been shown to be useful in the management of recurrent rectal cancer [73–78]. For primary rectal cancer, there may be some benefit in terms of the detection of distant metastases, but to our knowledge there has been only one study [79] that focused on nodal staging, and a disappointingly low sensitivity of 29% was reported in that study. The reason for the low sensitivity may well be that the proximity of the primary tumour to the urinary bladder obscures small nodal metastases.

Recently, MR imaging with the use of ultrasmall superparamagnetic iron oxide (USPIO) contrast agents has shown promising results for staging nodal metastases. USPIO is a contrast agent that undergoes phagocytosis by the reticuloendothelial system (macrophages in normal lymph nodes). The use of USPIO results in shortening of the T2 relaxation time and in a decrease in signal intensity on gradient-echo images of normal lymph nodes owing to increased susceptibility artefacts. These MR properties are used to aid in the detection of micrometastases in small lymph nodes. In metastatic nodes, the reticuloendothelial system is displaced by tumour deposits and shows deficits in the uptake of USPIO. In patients with head and neck cancer and urologic pelvic tumours, sensitivities for detection have been reported to be good [80, 81]. At present, the value of MR imaging with USPIO in the detection of nodal metastases in rectal cancer patients is not clear and warrants further evaluation.

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Pre-Operative Staging: Endorectal Ultrasound

Giulio Aniello Santoro, Carlo Ratto

Introduction

The great transformation in the management of rectal cancer has increased the importance of accurate pre-operative staging in decision-making. Depth of penetration and nodal status in rectal neoplasms guide therapeutic decisions to perform local excision or transanal endoscopic microsurgical excision, to take the patient directly for radical surgery or to offer neoadjuvant chemoradiotherapy. Of the available technologies, namely computed tomography (CT), magnetic resonance imaging (MRI), endoluminal coil MRI and endorectal ultrasound (ERUS), the latter has evolved as the best modality for accurately staging rectal cancer. ERUS has many advantages over CT and MRI. First the ERUS probe is placed in close proximity to the area of interest and the resolution and imaging quality are thus greatly enhanced. Second, it is an office-based procedure of short duration and is well tolerated by patients. Third, it is relatively low cost.

Equipment

The most widely used ERUS system is the Bruel and Kjaer scanner (Hawk 2102 EXL, B-K Medical A/S, Mileparken 34, DK-2730 Herlev, Denmark) with a hand-held rotating endoprobe type 1850, which gives a 360° axial view of the rectal wall (Fig. 1) [1]. The radial probe has a 24-cm metal shaft with a rotating transducer at its tip. This 8539 transducer has a frequency range from 5 to 10 MHz with a focal length of 2–5 cm and a 90° scanning plane and is rotated at 4–6 cycles/s to get a radial scan of the rectum and surrounding structures. The end of the probe is covered with either a latex balloon or a plastic cap that is filled with degassed water to maintain acoustic coupling between the transducer and the tissue (Fig. 2). It is important to eliminate all bubbles within the hard anal cap or the balloon, given that these may produce artefacts and limit the overall utility of the study. The latex balloon is chosen when imaging rectal cancers. The rectum can be of varying diameters and therefore the volume of water in the balloon may have to be adjusted intermittently. If the anus is being evaluated, a water-filled hard plastic cone, made of a sonolucent polymethyl pentene plastic and 1.7 cm in outer diameter, is used in place of the latex balloon. The outer walls of this cone are parallel, so that the probe may be moved within the anal canal without causing any anatomical distortion.

Technology progress allows the three-dimensional (3D) reconstruction of two-dimensional (2D) images [1]. It is not necessary to use new ultrasound probes, but to connect the ultrasound apparatus to a computer equipped with software (L3Di-2000/2100). Three-dimensional reconstruction is based on a high number of parallel transaxial images acquired using a special colorectal pullback mover (UA0552) with the B-K Medical ultrasound probe type 1850. The colorectal pullback mover is a computer-controlled, motor-driven device that can be operated at different

Fig. 1. B-K Medical anorectal probe type 1850

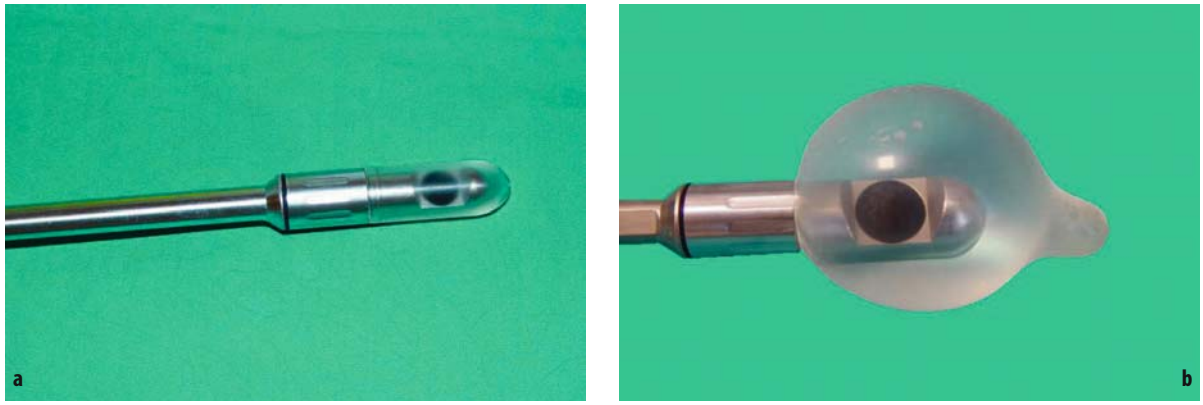

Fig. 2a, b. Contact methods: **a** plastic cone and **b** latex balloon

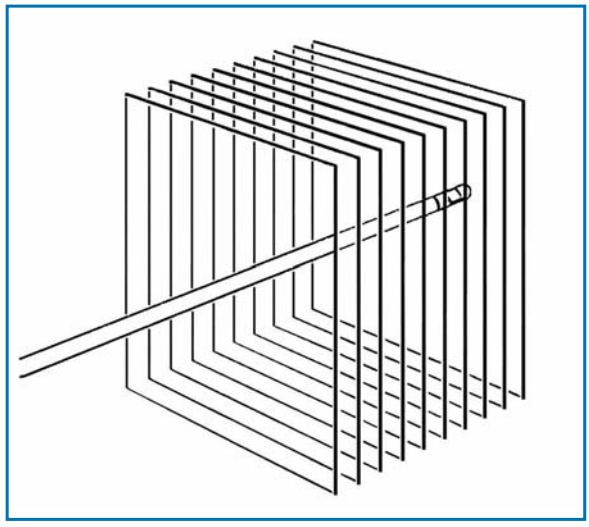

Fig. 3. Schematic model for acquisition of 3-D anorectal endo-image as parallel transverse 2D images

Fig. 4. B-K Medical anorectal transducer type 2050

levels of resolution. For the endo-anal application, the usual setting is 0.2–0.3 mm between adjacent transaxial images. Scanning the anal canal with these settings over a pullback distance of 35 mm will typically yield 175 parallel images. The data from a series of closely spaced 2D images is combined to create a 3D volume displayed as a cube (Fig. 3). The 3D image does not remain fixed, but rather can be freely rotated, rendered, tilted and sliced to allow the operator to infinitely vary the different section parameters and visualise the lesion at different angles and to get the most information out of the data. After data are acquired it is immediately possible to select coronal anterior–posterior or posterior–anterior as well as sagittal right–left views. The multiview function allows up to six different and specialised views to be seen at once with real-time reconstruction. Extensive anorectal examinations require moving the transducer head. Probe movement can cause artefacts and change anatomical presentation. The new B-K Medical 2050 anorectal transducer is designed so that no moving parts come into contact with human tissue (Fig. 4). The transducer's 360° rotating head, the proximal–distal actuation mechanism and the electronic mover are fully enclosed within the housing of the slim probe. Both 3D data set acquisition and high precision positioning of the scan head over a longitudinal distance of 60 mm are accomplished at the touch of a button, allowing the information to be obtained without having to move the probe's position. The 2050's double crystal covers a frequency range from 6 to 16 MHz. With a shaft length of 270

mm, the probe is long enough to thoroughly cover the entire rectum plus the sigmoideum.

Technique

Endoluminal ultrasound is usually performed with the patient in the left lateral decubitus position. Before the probe is inserted into the rectum, a digital rectal examination may be performed to identify the size, fixation, morphology and location of the tumour, if it is low enough. If there is a stenotic annular lesion, the finger can check to determine whether it will allow easy passage of the probe. The entire shaft of the probe is coated with a thin layer of warm gel using a paper towel. The probe tip is gently inserted through the anal canal and then angled posteriorly and advanced cephalad to as high a level as possible, with the bony sacrum used as a curved landmark. The patient should be instructed before the examination that no pain should be experienced. If pain should occur, the study should be halted until the cause of the pain is elucidated. Under no circumstances should force be used to advance the probe. The examiner should never try to push the tip through a narrow stenotic lesion. However, in most instances passage can be achieved, although the volume of the fluid in the balloon will have to be substantially reduced in order to withdraw the probe through the stenotic portion. Once the tip is advanced to as high a level as possible, usually 10–14 cm from the anal verge, the balloon can be inflated with 50 ml of water. Now the rotating transducer is activated and the rectal wall visualised. When the spigot for introducing water into the balloon is pointing towards the ceiling, by convention the anterior aspect of the rectum will be superior (12 o'clock) on the screen, right lateral will be left (9 o'clock) on the screen, left lateral will be right (3 o'clock) on the screen and posterior will be inferior (6 o'clock) on the screen (just like the image on axial CT scan). The tip of the ultrasound probe should be maintained in the centre of the rectal lumen to gain optimal imaging of the rectal wall and perirectal structures. Some adjustments may have to be made in the gain of the ultrasound unit to provide optimal imaging. Occasionally, it is possible to perfectly depict all five layers of the rectum circumferentially, but usually only a portion of the rectal wall can be optimally imaged at a time and minor adjustments will have to be made in the location of the probe relative to the rectal wall at various locations to optimally image all five layers clearly. The amount of water in the balloon may have to be increased to provide complete acoustic coupling with the rectal wall. The examiner should never distend the balloon with more than 80 ml of degassed water, as it may rupture. If this occurs, the probe must be removed from the rectum and cleaned, a new balloon installed and the whole procedure started over. If air or stool gets between the balloon and rectal wall, it will prevent visualisation of the wall. To avoid this we administer an enema 2 hours before the examination. Despite this, problems can arise and it may be necessary to remove the probe and suction out the rectum with reintroduction in order to optimise the image.

With the probe at the highest level possible and with good visualisation of the rectal wall, images are obtained at 1-cm intervals as the probe is withdrawn. The exact level of the transducer tip can be read off the metal shaft of the ultrasound probe. More closely spaced images (0.5 cm) are obtained in the area of any abnormality. The balloon may have to be deflated and reinflated to maintain good acoustic contact with the rectal wall as the probe is withdrawn down the rectum. Once the entire rectum down to the anal sphincter has been evaluated, the balloon is fully deflated and the probe is removed from the rectum. The entire length of the rectal tumour is carefully examined and it is not uncommon to require several passes along the full length of the tumour to gain all the information that is necessary. In some instances, two to six passes may be required to properly stage a rectal cancer. In most instances the use of a large bore proctoscope serves several purposes (Sapimed, Alessandria, Italy) (Fig. 5). It allows visual examination of the rectal tumour with exact determination of its location both with respect to circumferential involvement of the rectal wall and the distance from the anal verge. Secondly it allows suctioning of any residual stool or enema fluid that might interfere with the acoustic pathways of the ultrasound waves which may distort the image. Most importantly, however, it allows easy passage of the probe above the tumour to insure that the transducer is advanced above the rectal lesion to allow complete imaging of the rectal tumour. This is of extreme importance as the lower border of a rectal cancer can differ significantly in the depth of invasion to the centre or upper portions of the cancer and lymph nodes in the perirectal region are often just above the level of the tumour and will be missed if complete imaging is not obtained. Small distal lesions can be adequately imaged with the ultrasound inserted blindly and advanced above the lesion, but for most mid-rectal tumours, the use of a proctoscope will facilitate the passage of the transducer. Once the 20 cm scored mark on the shaft of the probe is at the proximal end of the proctoscope, the proctoscope is then pulled back on the probe as far as possible thus exposing the transducer for 7 cm beyond the end of the proctoscope and thus positioned above the rectal cancer.

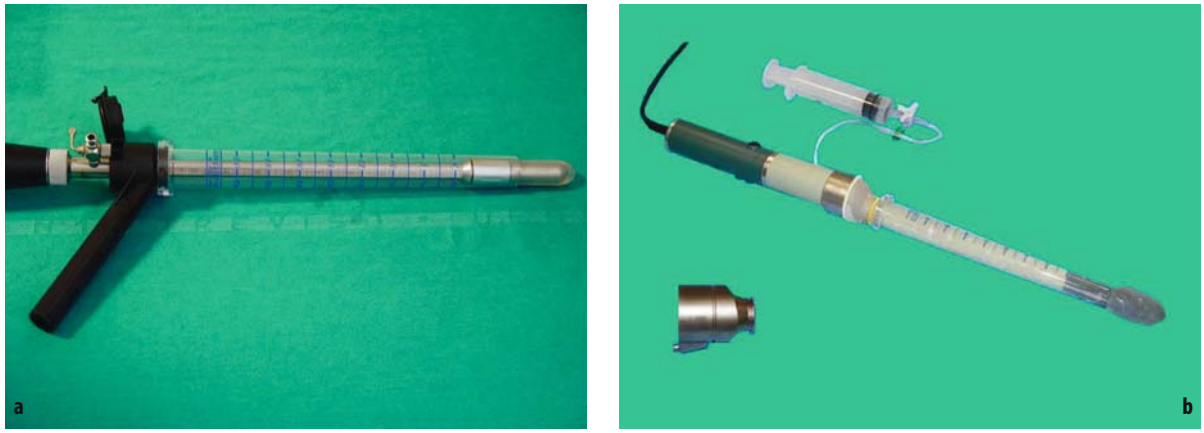

Fig. 5a, b. Dedicated proctoscope for endorectal ultrasonography assembled with (**a**) 1850 probe or (**b**) 2050 probe

The balloon is then instilled with 30–60 cc of water, the volume of fluid usually needed to gain optimal imaging.

Ultrasound Anatomy

On ultrasound the normal rectal wall is 2–3 mm thick and is composed of a five-layer structure [2] (Fig. 6). The first hyperechoic layer corresponds to the interface of the balloon with the rectal mucosal surface, the second hypoechoic layer to the mucosa and muscolaris mucosa, the third hyperechoic layer to the submucosa, the fourth hypoechoic layer to the muscolaris propria and the fifth hyperechoic layer to the serosa or represents the interface of the rectum with the perirectal fat. Good visualisation depends on maintaining the probe in the centre lumen of the rectum and having adequate distension of the water-filled balloon with good acoustic contact with rectal wall.

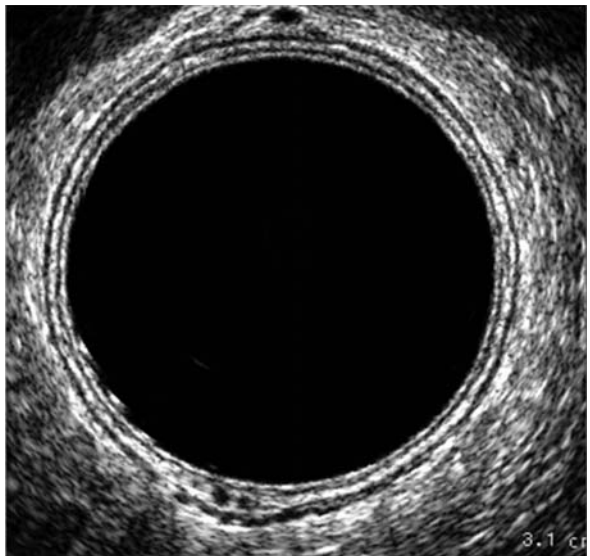

Fig. 6. Bidimensional ultrasonographic five-layer structure of the normal rectal wall

The ultrasonographer must have a clear understanding of what each of these five lines represent anatomically. When staging a rectal cancer, various levels of the tumour must be optimally imaged and the integrity of the lines carefully assessed. Attention must be focused on the third hyperechoic layer. Once it has been ascertained that the middle hyperechoic line is broken, then an invasive lesion is recognised and attention is then turned to the thickness of the muscolaris propria and the integrity of the outer hyperechoic line to see if the perirectal fat is invaded. The fibrofatty tissue surrounding the rectum contains blood vessels, nerves and lymphatics and has an inhomogeneous echo pattern. Very small, 2–3-mm, round to oval hypoechoic lymph nodes may be seen and must be distinguished from blood vessels, which are also circular hypoechoic areas, but when followed longitudinally, they seem to extend further than the corresponding diameter and can often be seen to branch and to elongate in a longitudinal fashion, confirming that this is a blood vessel and not a node. Anteriorly the bladder, seminal vesicles and prostate can be identified in the male and the uterus, cervix and vagina in the female.

Three-dimensional ERUS offers a valuable supplement to conventional ultrasound. The 5 layers of the rectal wall are clearly illustrated in the coronal plane as well as in the transaxial and the longitudinal image planes (Fig. 7).

Endoluminal ultrasound defines anatomy of the anal canal and pelvic floor. Five and possibly six hypoechoic and hyperechoic layers can be seen [2].

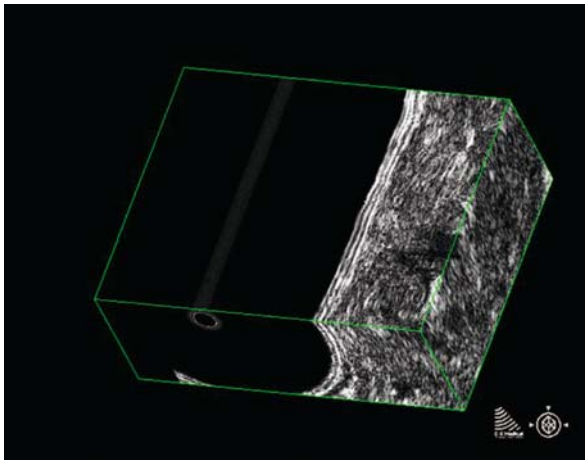

Fig. 7. Three-dimensional ultrasonographic five-layer structure of the normal rectal wall

From inner to outer, the first hyperechoic layer corresponds to the interface of the plastic cone with the anal mucosal surface, the second hypoechoic layer to the mucosa, the third hyperechoic layer to the subepithelial tissues, the fourth hypoechoic layer to the internal anal sphincter (IAS), the fifth hyperechoic layer to the longitudinal muscle (LM) and the sixth mixed echogenic layer to the external anal sphincter (EAS) (Fig. 8). The hypoechoic layer that represents the IAS can be traced superiorly into the circular muscle of the rectum. Its thickness varies from 1.5 to 4 mm (mean 3.5±0.5 mm) and increases with age owing to the presence of more fibrous tissue as the absolute amount of muscle decreases. The LM is 2.5±0.6 mm in males and 2.9±0.6 mm in females. This muscle is moderately echogenic, which is surprising as it is mainly smooth muscle, however an increased fibrous stroma may account for this. The average thickness of the EAS is 8.6±1.1 mm in males and 7.7±1.1 mm in females, respectively. The thickness of the IAS and the EAS should be measured at the 3 and 6 o'clock positions in the midlevel of the anal canal.

Ultrasound imaging of the anus can be divided into three levels: deep, mid and superficial portions [2]. The level refers to the following anatomical structures: (1) deep: the sling of the puborectalis and the deep part of the external sphincter; (2) mid: the anococcygeal ligament, superficial part of the external sphincter, internal sphincter and perineal body and (3) superficial: the subcutaneous part of the external sphincter. The first ultrasound image recorded is normally at puborectalis level, where the perineal body is also seen in females. This image is normally documented and labelled high. In a normal patient, moving the probe a few millimetres in the distal direction will show an intact anterior EAS forming just below the superficial transverse perineal muscles. This image is a mid-canal projection where the IAS, conjoining LM and the superficial EAS all are identified. This image will be labelled mid. When the probe is pulled further out, the image of the IAS will disappear and only the subepithelium and the subcutaneous segment of the LM+EAS will be seen. This last image will be labelled low.

Rectal Cancer Staging

ERUS criteria to determine the depth of tumour invasion, based on the classification proposed by Hildebrandt and Feifel [3], are as follows: (a) uT0 (benign lesion): the mucosal layer is expanded but the third hyperechoic submucosal layer remains intact around the entire breadth of the tumour; (b) uT1 (submucosal cancer): the hyperechoic submucosal layer is

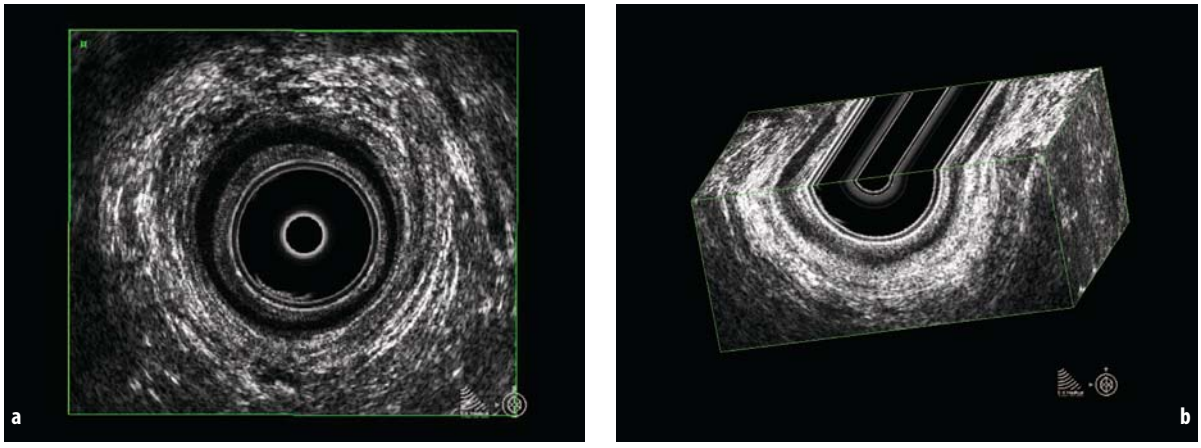

Fig. 8a, b. Normal ultrasound anatomy of the anal sphincter in 2D (**a**) and 3D (**b**)

irregular or interrupted consistent with tumour invasion. The fourth hypoechoic layer of the muscolaris propria is intact; (c) uT2: a distinct break is seen in the submucosal layer and the muscolaris propria is thickened. The surrounding hyperechoic layer corresponding to the serosa or perirectal fat remains intact; (d) uT3: disruption of the hyperechoic layer corresponding to the submucosa, thickening of the hypoechoic layer representing the muscolaris propria and presence of irregularities of the outer hyperechoic layer which corresponds to the serosa or perirectal fat interface; and (e) uT4: extensive local invasion with loss of the normal hyperechoic interface between tumour and the adjacent organ or invasion of the serosa in tumours above the peritoneal reflection.

Undetectable or benign appearing lymph nodes are classified as uN0. Pathologic lymph nodes are defined as circular or slightly oval-shaped structures, often with an irregular border, with an echogenicity similar to the tumour and most commonly found adjacent or in the mesorectum proximal to the primary tumour. Malignant appearing lymph nodes are classified as: (a) uN1: <3 malignant lymph nodes identified, and (b) uN2: >3 malignant lymph nodes identified.

Stage uT0: Villous Adenoma

Sonographic evaluation of a villous rectal lesion is helpful in determining the presence of tumour invasion. The presence of an intact hyperechoic submucosal interface indicates lack of tumour invasion into the submucosa. Heintz et al. [4] believe that ERUS cannot differentiate between villous adenoma and invasive cancers because neither the muscolaris mucosae nor the submucosa is sonographically definable and the first hypoechoic layer corresponds anatomically with the mucosa and the submucosa. They suggest that uT0 and uT1 tumours, which manifest as a broadening of the first hypoechoic layer, should be classified together. Instead Adams and Wong [5] disagree with this interpretation and consider the first hypoechoic layer as the mucosa and muscolaris mucosae and the middle hyperechoic layer as the submucosa. Consequently for such Authors lesions that expand the inner hypoechoic layer and are surrounded by a uniform middle hyperechoic layer are considered villous adenoma (Fig. 9) and lesions that expand the inner hypoechoic layer and have distinct echo defects of the middle hyperechoic layer are considered uT1 tumours. Technical difficulties associated with scanning villous adenoma can be due to very large lesions that tend to attenuate rectal layers and lesions with a very large exophytic component. In large carpeting lesions, careful evaluation of the entire tumour is necessary to determine that a small area of invasion has not been overlooked. In some polyps the complex structure produce fixed artefacts over one part of the rectal wall, obscuring the image. Snare biopsy of lesions before referral to ERUS produces a burn artefact, which can lead to tumour overstaging.

Stage uT1: Submucosal Invasion

If a tumour arises in a polyp it is important to determine whether the stalk is invaded. Differences in classification are reported between Western and Japanese pathologists. In 1985 Haggitt et al. [6] divid-

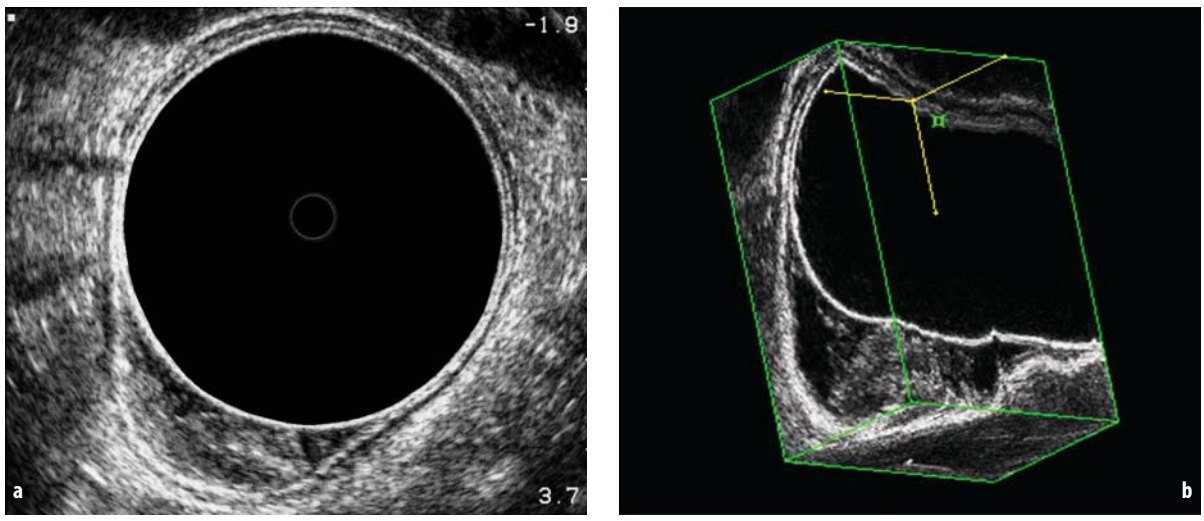

Fig. 9. uT0 rectal tumour (villous adenoma) in 2D (**a**) and 3D (**b**)

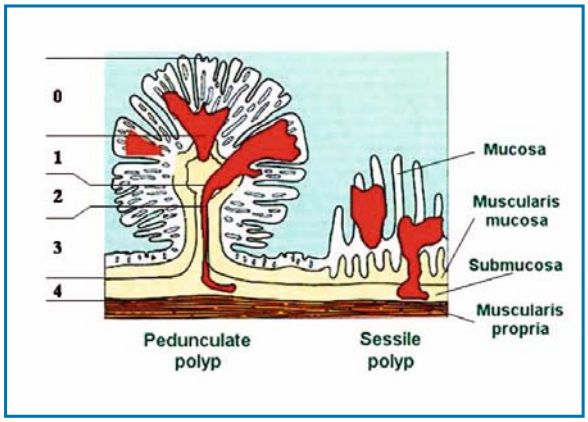

Fig. 10. Level of submucosal invasion according to Haggitt's classification

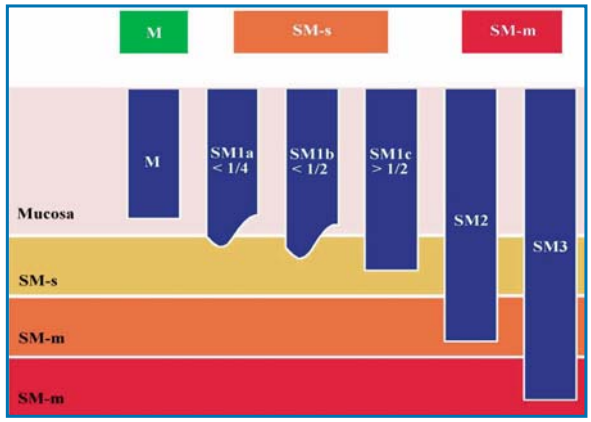

Fig. 11. Level of submucosal invasion according to the Japanese classification

ed the depth of invasion into four levels: Level 0, carcinoma *in situ* or intramucosal carcinoma; Level 1, carcinoma invading through the muscolaris mucosa into the submucosa but limited to the head of the polyp; Level 2, carcinoma invading the level of the neck of the adenoma; Level 3, carcinoma invading any part of the stalk; Level 4, carcinoma invading into the submucosa of the bowel wall below the stalk of the polyp. By definition all sessile polyps with invasive adenocarcinoma are Level 4 (Fig. 10). They studied 129 patients with pTis to pT1 colorectal tumours and found that Level 4 invasion was a statistically significant factor ($p<0.001$) predicting positive nodes. Similar results were reported by Nivatvongs et al. [7] on 151 patients with pT1 colorectal tumours undergoing bowel resection in which invasion into the submucosa of the bowel wall at the base of the stalk (Level 4) was the single most significant risk factor for positive nodes. For sessile polyps the risk was 10% and for pedunculate polyps 27%. Suzuki et al. [8] determined the risk of lymph node metastases in 65 patients having Haggitt's Level 4 invasion into the submucosa. Lymph node metastasis was noted in 11 (16.9%) of the 65 patients, however the width of submucosal invasion was significantly greater in node-positive than in node-negative patients ($p=0.001$). When 5-mm-wide submucosal invasion was used as an indicator for intestinal resection, 37 patients were found to have indications for bowel resection and 11 (29.7%) of the 37 had lymph node metastases. The positive predictive value increased from 17 to 30% when the width of submucosal invasion was added to Haggitt's Level 4 as an indicator for bowel resection. Seitz et al. [9] suggested that Haggitt's classification applies well for pedunculate polyps, however it should not be used for malignant sessile polyps.

Kudo et al. [10] were the first to differentiate three different types of early invasive cancers: (1) SM-1 tumour, invading the superior third of the submucosa, (2) SM-2 tumour, invading the superficial two thirds of the submucosa, and (3) SM-3 tumour, invading the deep third of the submucosa. Within the group type SM-1, there are three subtypes: type SM-1a (indicates that invasion is <1/4 of the submucosa), type SM-1b (indicates that invasion is <1/2 of the submucosa) and type SM-1c (indicates that invasion is >1/2 of the submucosa). Kikuchi et al. [11] found that the risk of lymph node metastasis was 0% for SM-1 lesion, 10% for SM-2 lesions and 25% for SM-3 lesions ($p<0.001$). In their study the SM-3 was the only independent risk of lymph node metastasis.

Akasu et al. [12] recently proposed a classification of the depth of submucosal cancer into two groups: (1) SM-slight (SM-s), extent limited to the upper third of the submucosa; and SM-massive (SM-m), tumour invasion extended to the middle or lower third of the submucosa (Fig. 11). In their series, incidences of lymph node metastasis in pTis, pT1-slight and pT1-massive were 0%, 0% and 22%, respectively. Thus massive submucosal invasion can be considered a risk factor for lymph node metastasis. They suggested that patients with massive submucosal invasion are best treated by radical surgery. A recent study from the Mayo Clinic confirms these data [13]. Among patients with T1 carcinoma in the middle or lower third of the rectum the multivariate risk factors for long-term, cancer-free survival was invasion into the lower third of the submucosa. For lesions with SM3 invasion, the oncologic resection group had lower rates of distant metastasis and better survival compared with patients who underwent local excision. Therefore a decision whether to perform radical surgery or local excision or polypectomy should be

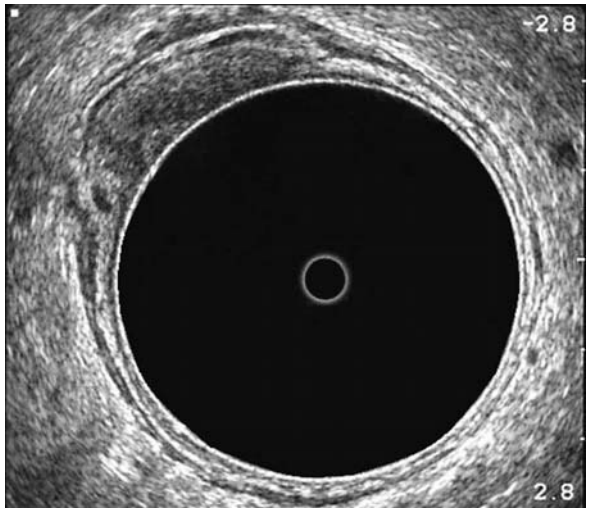

Fig. 12. uT1 rectal tumour

based principally on assessment of invasion depth.

Our ERUS criteria to determine the depth of tumour invasion are as follows: (a) benign lesions (uT0), the mucosal layer is expanded but the submucosal layer remains intact around the entire breadth of the tumour; (b) mucosal or intramucosal neoplasia (M) (uTis), presence of echo-poor spots within the homogeneously echo-rich pattern of villous adenoma. The third hypoechoic layer representing the submucosal interface is intact; and (c) submucosal cancer (uT1), the hyperechoic submucosal layer is irregular or interrupted, consistent with tumour invasion (Fig. 12). The depth of submucosal cancer invasion is classified into two subtypes: slight (SM-s: extent limited to the upper third of the third layer. The fourth hypoechoic layer of the muscolaris propria is intact) and massive (SM-m: tumour invasion extended to the middle or lower third of the third layer. The fourth hypoechoic layer is thickened consistent with peritumoral inflammation and desmoplastic reaction). If a distinct break is seen in the submucosal layer, the muscolaris propria has been invaded (uT2 lesion).

Over- and understaging of rectal tumours continues to be a problem in staging with ERUS due to a variety of well documented causes as reported by Adams and Wong [5] and Kim et al. [14]. A source of error can be due to the compression of the rectal wall by the water-filled balloon. To prevent any distortion of the lesion or separation of the balloon from the rectal wall with the interposition of non-conductive air between the probe and the rectum, a sufficient quantity of water can be instilled to fill the entire rectum. In this case the transducer is covered with a sonolucent plastic cap that does not cause compression of the rectal wall as with the balloon. A source of errors in the evaluation of early rectal cancer by ERUS can also frequently be caused by examiner confusion or a tendency to overestimate a malignant lesion because of concern for undertreatment despite clear ERUS imaging.

Stage uT2: Invasion of the Muscular Layer

Sonographic diagnosis of tumour invasion of the muscolaris propria is based on thickening of this layer (Fig. 13). The muscolaris propria is represented by a thin hypoechoic layer adjacent to the hyperechoic submucosal interface. As the tumour is also hypoechoic, early muscular invasion is difficult to

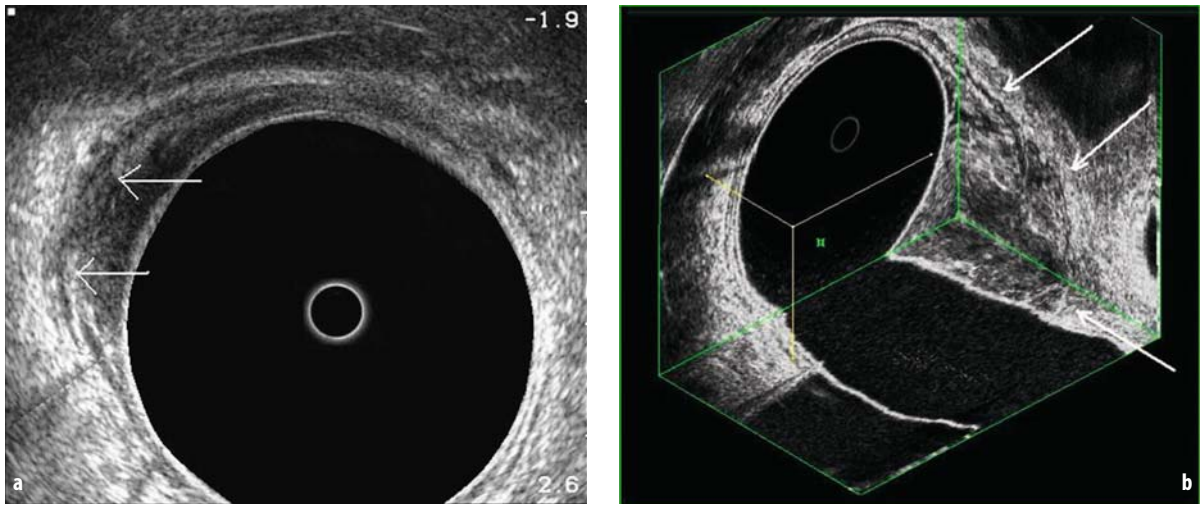

Fig. 13a, b. uT2 rectal tumour in 2D (**a**) and 3D (**b**)

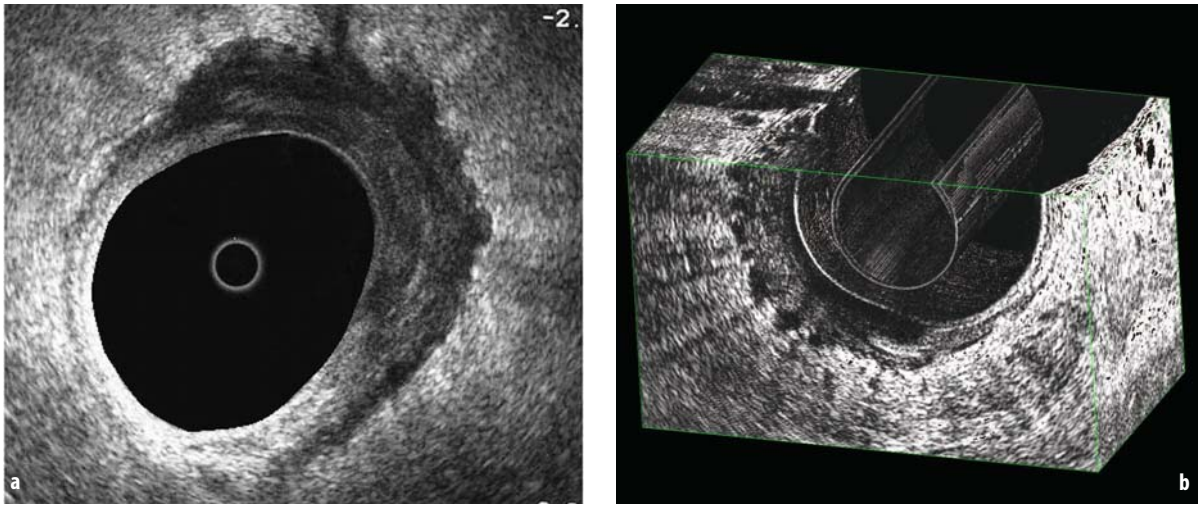

Fig. 14a, b. uT3 rectal tumour in 2D (**a**) and 3D (**b**)

detect. The surrounding hyperechoic layer corresponding to the perirectal fat interface remains intact. Lymph node metastases occur in approximately 15–20% of patients with T2 tumours. ERUS is important to distinguish uT2 and uT1 lesions, because local therapy is not routinely recommended for uT2 rectal lesions.

Overstaging is a particular problem with T2 tumours. Among the interpretative errors, severe inflammatory infiltrate underlying a tumour, which is sonographically indistinguishable from malignant tissue, can prohibit accurate evaluation of tumour invasion and appears to cause inevitable error. Understaging, on the other hand, may be caused by a failure to detect microscopic cancer infiltration owing to the limits of resolution of the equipment.

Stage uT3: Perirectal Fat Invasion

Perirectal fat invasion is diagnosed sonographically by the presence of irregularity of the outer hyperechoic layer that corresponds to the perirectal fat interface (Fig. 14). These findings should be associated with disruption of the hyperechoic layer corresponding to the submucosa and thickening of the hypoechoic layer representing the muscolaris propria. Contiguous organs are not involved. About 10% of such tumours are unfortunately accompanied by a narrowing of the lumen and angulation and it may be difficult or impossible to advance the probe proximal to the tumour (Fig. 15). To perform a complete staging by ERUS, a residual lumen of 2 cm is necessary because only those structures seen at a 90° angle to the probe can be assessed correctly. Under these circumstances the study may be incomplete and the presence of enlarged lymph nodes may not be ascertained with accuracy because nodes are often located proximal to the tumour. The incidence of regional lymph node metastases in uT3 tumours is approximately 30–50%.

The recognition of perirectal fat invasion is an important determination to select appropriate patients for pre-operative combined chemotherapy and radiation therapy followed by surgery. One of the most important drawbacks in endosonographic staging is the distinction between T2 tumour invading most of the muscolaris propria and T3 tumour which slightly invades the perirectal fat. Indeed most errors are understaging of small pT3 tumours or overstaging of pT2 tumours [15].

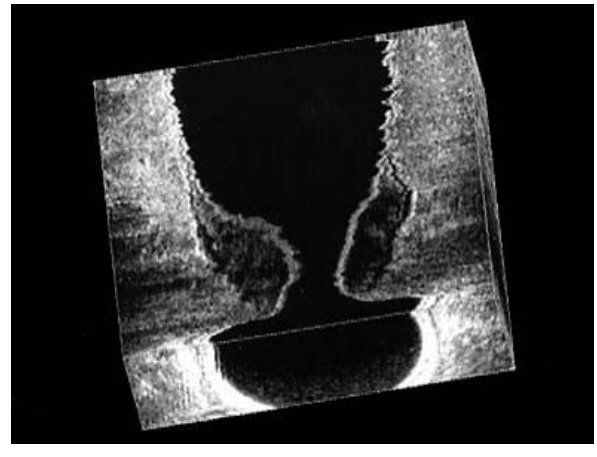

Fig. 15. Three-dimensional ERUS showing a tumour that narrows the rectal lumen

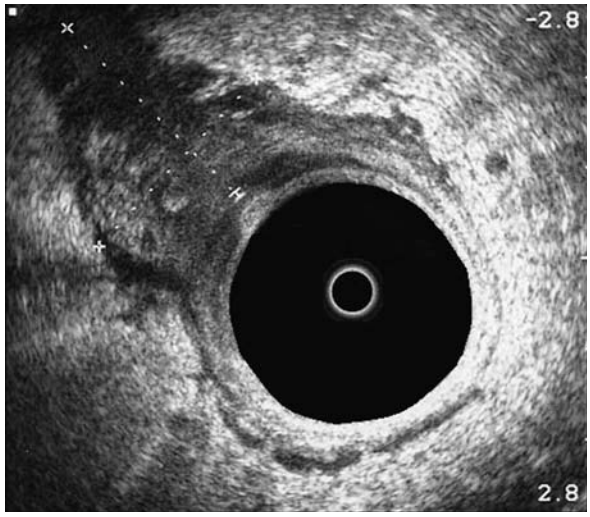

Fig. 16. uT4 rectal tumour

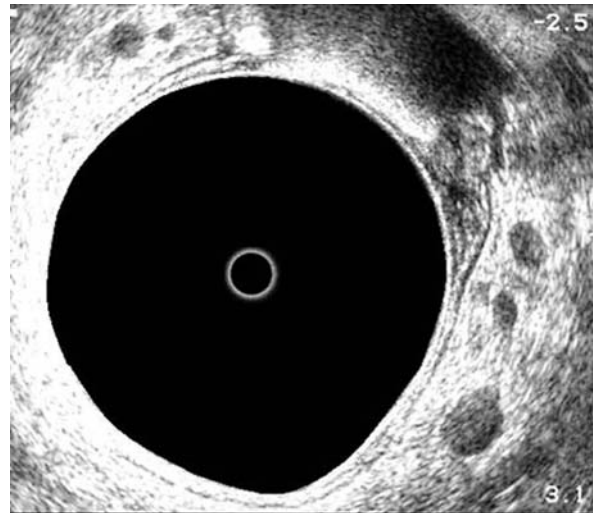

Fig. 17. Sonogram of an enlarged, hypoechoic lymph node appearing as a possible nodal metastases

Stage uT4: Extensive Local Invasion

uT4 lesions are locally invasive into contiguous organs such as bladder, uterus, cervix, vagina, prostate and seminal vesicles. These advanced lesions are clinically fixed or tethered. Sonographically there is a loss of the normal hyperechoic interface between tumour and the adjacent organ (Fig. 16). The inability of ERUS to distinguish between malignant infiltration or peritumoral inflammation results in a somewhat lower staging accuracy with regard to T4 cancers. Frank stenosis also precludes precise endosonographic evaluation and angulation of the probe to the tumour axis also can cause misinterpretation.

Stage uN1–2: Lymph Node Metastases

Metastatic involvement of the mesorectal lymph node is a major independent prognostic factor. It has been observed that the presence of >3 nodes is associated with a poor prognosis. Moreover, identification of a metastatic perirectal lymph node is important as these patients may benefit from pre-operative adjuvant radiotherapy and some of the early T1 or T2 lesions with mesorectal node involvement are not suitable for local excision.

Sonographic evaluation of lymph node metastases is somewhat less accurate than depth of invasion [15]. Undetectable or benign appearing lymph nodes are classified as uN0. Malignant appearing lymph nodes are classified as uN1 (<3 lymph nodes) or uN2 (>3 lymph nodes). Normal, non-enlarged perirectal nodes are not usually seen on ERUS. The criteria used to identify metastatic lymph nodes in most of the studies are echogenicity, border demarcation and node diameter. Inflamed, enlarged lymph nodes appear hyperechoic, with ill defined borders. Much of the sound energy is reflected because the lymphatic tissue has not changed. In contrast, metastatic lymph nodes that have been replaced with tumour do not provide the normal tissue architecture and appear hypoechoic with an echogenicity similar to the primary tumour (Fig. 17). Malignant lymph nodes tend to be circular rather than oval, have discrete borders and are most commonly found adjacent to the primary tumour or in the mesorectum proximal to a tumour (Fig. 18). The sonographic features of lymph nodes generally can be distributed into four groups. If lymph nodes are not visible by ultrasound, the probability of lymph node metastases is low. Hyperechoic lymph nodes are often benign and result from non-specific inflammatory changes. Hypoechoic lymph nodes larger than 5 mm are highly suggestive for lymph node metastases. Lymph nodes larger than 5 mm that are visible with mixed echogenic patterns cannot be classified accurately but should be considered metastatic. On size characteristics alone, sonographically detected nodes in the mesorectum greater than 5 mm in diameter have a 50–70% chance of being involved, whereas those smaller than 4 mm have a less than 20% chance. However, up to 20% of patients have involved nodes of less than 3 mm, limiting the accuracy of the technique. Hulsmans et al. [16] studied several features by correlating pathologic and sonographic findings in the lymph nodes of specimens

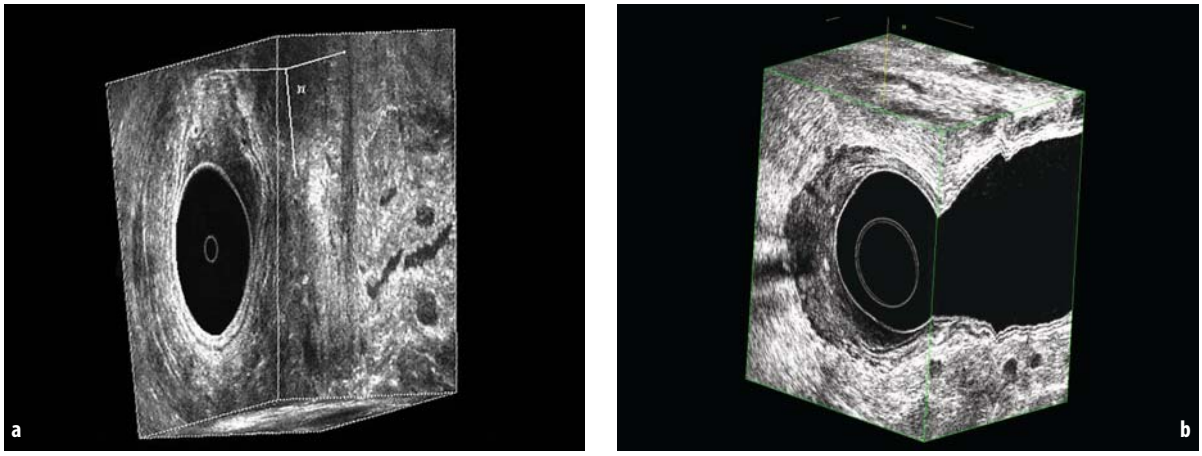

Fig. 18a, b. Three-dimensional ERUS showing malignant lymph nodes

obtained from a series of 21 consecutive patients with resected rectal cancer. These features included ratio of long axis to short axis diameter, referred to as roundness index; lobulations (multiple notches); echogenicity; inhomogeneity (not uniform); border delineation; presence of an echo-poor rim (the outer rim being more hypoechoic than the rest of the node); presence of a peripheral halo; and presence of a hilar reflection. The Authors showed that 3 ultrasonographic features of a node significantly related to its being benign or malignant at histopathologic examination are short axis diameter, degree of inhomogeneity and presence or absence of hilar reflection.

Overstaging and understaging can occur during assessment of lymph node involvement. Oedematous lymph nodes transmit more sound energy and appear in echo patterns that are similar to metastases. The cross-sectional appearance of blood vessels in the perirectal fat may be commonly confused with positive lymph nodes. The sonographic continuity of hypoechoic vessels over a distance greater than the cross-sectional diameter is the criterion used to distinguish vessels from hypoechoic lymph nodes. With careful scanning, blood vessels appear to branch or extend longitudinally. In addition, it may be difficult to differentiate islands of tumour outside the bowel wall from involved nodes. With careful scanning, one can demonstrate continuity with the main tumour that may not have been recognised initially. Even with an improved understanding of the characteristic of malignant lymph node and utilising criteria of shape, echogenicity and border character, micrometastases and granulomatous inflammation likely will be difficult if not impossible to differentiate by ERUS. If a whole node is replaced by tumour or the node is enlarged secondary to it, detection is more likely. However, if only a small deposit or a micrometastasis is present in a node, the characteristics of the node are unlikely to be sufficiently altered to allow detection. This explains in part the lower accuracy rates for lymph nodal detection with current, conventional ultrasonography. Grossly malignant lymph nodes located a distance from the primary tumour also remain undetected if they exceed the depth of penetration of the transducer. This is particularly true of nodes in the proximal mesorectum above the reach of the rigid probe. To obtain high sensitivity and high specificity, the combination of a small cutoff value and ERUS-guided needle biopsy or ERUS-guided fine-needle aspiration biopsy may be helpful.

Accuracy

Most of the studies have reported the accuracy rates of ERUS in the evaluation of rectal tumour invasion to be 81–94% (Table 1) [15]. Overestimation occurred in 10% of cases and underestimation occurred in 5% of cases. The accuracy of ERUS in assessing the depth of rectal wall invasion varies with tumour stage. In the literature ERUS remains the most accurate technique for determining the depth of tumour invasion in early stage rectal cancer. Garcia-Aguilar et al. [17], from the Division of Colon and Rectal Surgery at the University of Minnesota, reported that ERUS correctly staged most villous adenomas (accuracy: 87%) but less than half of T1 tumours (accuracy: 47%). However in a systematic literature review Worrell et al. [18] reported that ERUS correctly established a cancer diagnosis in 81% of 62 biopsy-negative rectal adenomas which had focal carcinoma on histopathology. In another study

Table 1. Accuracy of endorectal ultrasonography (ERUS) in determining depth of rectal wall invasion of rectal tumours

Authors	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overstaged (%)	Understaged (%)
Herzog et al. [33]	98.3	75	89.2	95.4	10.2	0.8
Sentovich et al. [31]	79	–			17	4
uT2			81	88		
uT3/T4			90	100		
Glaser et al. [28]	pT3: 97	pT3: 90	90	pT3: 98	–	–
Holdsworth et al. [29]	96	50	87	80	–	–
Hulsmans et al. [16]	97	24	–	–	–	–
Beynon et al. [30]	97	92	–	–	–	–
Garcia-Aguilar et al. [17]	–	–	72	93	18	13
Akasu et al. [12]						
Early pT1	99	74	97	87	–	–
Deep pT1	98	88	98	88	–	–
pT2	97	93	97	90	–	–
pT3	96	83	85	96	–	–
Sailer et al. [25]						
pT0/T1	81	98	–	–	–	–
pT2	41	92				
Kim et al. [14]						
pT0	83.1	96.5	–	–	27	11.2
pT1	93.3	97.9			15.7	5.6
Santoro et al. [15]	82	93	94	88	25	11

from the Cleveland Clinic Florida [19] the final pathology results confirmed the pre-operative ERUS diagnosis of rectal villous tumours without evidence of malignancy in 26 of 27 patients (96%). Akasu et al. [12] reported the results of a study on 154 patients with early stage rectal cancer pre-operatively evaluated by ERUS. Sensitivity, specificity and overall accuracy rates for detection of slight or massive submucosal invasion were 99%/74%/96% and 98%/88%/97%, respectively. Konishi et al. [20] reported that the overall accuracy of ERUS-based evaluation of tumour invasion depth was 60% in villous lesions and 91% in non-villous lesions. In differentiating mucosal neoplasias (M)/submucosal cancers with slight invasion (SM-s) from non-M/SM-s the accuracy of ERUS in villous and non-villous lesions was 66% and 96%, respectively. Akahoshi et al. [21] improved the accuracy of ERUS by using a high-frequency (12 MHz) ultrasound catheter probe. The depth of invasion was correctly assessed in 87% (46/53) of pT1 tumours. Starck et al. [22] reported their experience with high multifrequency probes. The sensitivity of ERUS with regard to invasion was 89% (16/18), specificity 88% (37/42) and accuracy 88% (53/60). They concluded that rectal endosonography can distinguish between benign rectal lesions and early invasive rectal cancers. Similar results were recently reported by Hunerbein et al. [23] with a high-frequency (12.5 MHz) miniprobe ultrasonography in the staging of colonic tumours. The infiltration depth was correctly classified in 78 of 88 patients (accuracy, 87%). We conducted a prospective study to compare the accuracy of 3D-ERUS with high-frequency ultrasound probe to conventional 2D-ERUS in the pre-operative staging of early invasive rectal cancer [24]. Eighty-nine consecutive patients with rectal villous lesions were examined using both 3D-ERUS and conventional 2D-ERUS. All lesions were resected either endoscopically or surgically. Histologically malignant transformation was found in 35 rectal villous adenomas. 2D-ERUS correctly determined the depth of invasion of villous polyps in 6 of 7 M neoplasias (85.7%), 8 of 12 SM-s lesions (66.6%) and 12 of 16 SM-m lesions (75%), whereas the accuracy of 3D-ERUS was 85.7% for M neoplasias, 83.3% for SM-s and 87.5% for SM-m lesions. Overall accuracy of the 2D-ERUS-based evaluation of villous lesions was lower than that of 3D-ERUS-based evaluation (27/35, 77.1%, vs. 30/35, 85.7%), however there was no significant difference (p=0.5). In the evaluation of SM-s lesions the accuracy of 3D-ERUS was significantly superior to 2D-ERUS-based evaluation (p<0.029). Tumour location and gross morphology (sessile or pedunculate) did not correlate with accurate T-staging. Eight of 54 pT0 tumours (14.8%) were overstaged by 2D-ERUS, while 5 of 54 (9.2%) were overstaged by 3D-ERUS. Incidences of lymph node metastasis in M, SM-s and SM-m lesions were 0%, 0% and 12.5%, respectively. The findings showed 3D-ERUS to have a significant advantage over 2D-ERUS

Table 2. Accuracy of endorectal ultrasonography (ERUS) in determining lymph node metastasis from rectal tumours

Author	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)
Hildebrandt et al. [3]	72	83	78	–	–
Herzog et al. [33]	89.2	73.4	80.2	71.2	90.4
Sentovich et al. [31]	100	100	–	–	73
Glaser et al. [28]	78	80	79	76	82
Holdsworth et al. [29]	57	64	61	50	70
Garcia-Aguilar et al. [17]	33	64	64	52	68
Akasu et al. [12]	100	60	65	26	100
Kim et al. [14]	53.3	75	63.5	70.6	58.8
Santoro et al. [15]	70	79	74	72	84

for the accurate evaluation of superficial submucosal cancer invasion. Stereoscopic visualisation provided easier and more complete understanding of depth of submucosal invasion.

Overstaging is a particular problem with T2 tumours. In a prospective study Sailer et al. [25] examined the value of ERUS in the pre-operative staging of 160 rectal tumours. For T2 tumours, the sensitivity was only 41% and the specificity 92% as the majority of pT2 neoplasias were overstaged (uT3). Authors concluded that ERUS is of no help in the assessment of T2 carcinomas. Katsura et al. [26] reported that the predictive value of positive rate in the assessment of rectal wall invasion by ERUS was 96.2% in uT1 and 87.5% in uT2. Three-dimensional ERUS offers a significant advantage over conventional bidimensional ERUS for the accurate evaluation of rectal cancer. In a preliminary study, Kim et al. [27] showed that the accuracy of 3D ERUS was 90.9% for pT2 whereas that of 2D-ERUS was 84.8%. Glaser et al. [28] reported that the sensitivity of ERUS for detection of perirectal fat infiltration (uT3) was 97%, specificity was 90%, negative predictive value was 98% and positive predictive value was 90%. The inability of ERUS to distinguish between malignant infiltration or peritumoral inflammation results in a somewhat lower staging accuracy with regard to T4 cancers.

The accuracy of ERUS in assessing lymph node involvement varies from 58% to 86% (Table 2) [15]. Holdsworth et al. [29] carried out endorectal sonography by means of a 5.5 MHz transducer. They identified lymph node metastases with a sensitivity of 57% and a specificity of 64% and concluded that the technique is not reliable to identify metastases. Beynon et al. [30], based on identification of circular or oval echo-poor lesions in the mesorectum, obtained a sensitivity of 86% and a specificity of 79% for detection of involved nodes. Kim et al. [27] reported that lymph node metastases were accurately predicted by 3D ERUS in 84.8% of patients, whereas 2D ERUS predicted the disorder in 66.7%. Although the findings did not show 3D ERUS to have a statistically significant advantage over 2D ERUS, stereoscopic visualisation provided easier and more complete understanding of lymph nodes.

Whether tumour site (in terms of height) and position (with respect to rectal circumference) have an influence on the reliability of endoluminal ultrasound staging is not settled as yet. Sentovich et al. [31] and Senesse et al. [32] reported a significantly better result for tumours within 6 cm of the anal verge. This is in contradiction to the study conducted by Herzog et al. [33] who found a significantly poorer accuracy rate for tumours of the distal third. The reason for the less accurate staging in the lower rectum is a technical one, that is the difficulty in reaching all sites of the ampulla recti with a rigid probe. This consideration prompted us to make a new dedicated rectoscope to allow easy passage of the probe above the rectal lesion. We performed a prospective study to determine if tumor site and tumor position have an influence on the accuracy of three-dimensional ERUS (3D-ERUS) staging [34]. Endorectal ultrasonography was performed on 173 consecutive patients with primary rectal cancer. In 65 patients the tumour was located 0.1–6 cm from the anal verge (lower rectal tumour), 77 patients had tumours 7–12 cm from the anal verge (middle rectal tumour) and 31 tumours were 13–18 cm from the anal verge (upper rectal tumour). With regard to position, 46 tumours were situated anteriorly, 30 in the left lateral rectal wall, 43 posteriorly and 42 in the right lateral rectal wall. In 12 patients the tumour occupied two-thirds of the rectal circumference. All lesions were resected either endoscopically or surgically. ERUS determined the depth of invasion in 62/65 (95.3%) lower rectal tumours, 74/77 (96.1%) middle rectal tumours and 28/31 (90.3%) upper rectal tumours. With regard to position, accuracy was

93.4% for tumours situated anteriorly, 90.4% for tumours in the right lateral position, 90.6% for tumours situated posteriorly and 86.6% for tumours in the left lateral position. The accuracy of 3D-ERUS for lymph node metastases, evaluated in 142 patients, was 44/46 (95.6%) for lower rectal tumours, 61/65 (93.8%) for middle rectal tumours and 28/31 (90.3%) for upper rectal tumours. Analysis showed that there was no difference between the various locations and positions, which means that all tumours are equally amenable to ultrasound staging if they are within reach of the scanner.

A number of comparative studies have been performed to assess the efficacy of endorectal ultrasonography, CT, MRI and digital examination in the pre-operative staging of rectal cancer. Some studies have shown a clear superiority for endorectal ultrasonography whereas other studies have shown little difference. CT and MR imaging are accurate in assessing spread beyond the rectal wall, invasion of contiguous structures, spread to regional nodes or distant metastases. The lateral pelvic lymph nodes, such as the obturator nodes, are located too far from the rectum to be imaged effectively with rectal probes. Therefore, possible advantages of MRI and CT can be considered in assessing the lateral pelvic lymph nodes, pelvic wall invasion and involvement of levator ani muscle. However, CT and MR imaging currently lack the accuracy in determining depth of wall invasion required by the surgeon. Overall accuracy of CT for the staging of rectal tumours is approximately 50–75%. Goldman et al. [35] compared CT with ERUS and found accuracy rates of 52% and 81% respectively, for perirectal fat invasion and 64% and 68% respectively, for lymph node involvement. Similarly, Beynon et al. [30] showed that ERUS was significantly more accurate than CT for both depth of tissue invasion and lymph node involvement. Accuracy rates were 68%, 82% and 91% for 44 patients evaluated with digital examination, CT and ERUS respectively. Civelli et al. [36] reported in the identification of neoplastic infiltration of perirectal fat (T3) endorectal balloon CT had 100% sensitivity, 78.7% specificity and 86.8% accuracy. The CT sensitivity for detecting lymph node metastases was 52.6%, specificity 85.3% and accuracy 73.6%. MRI with endorectal coils has been studied in a number of small studies for the evaluation and staging of rectal tumours [37]. With the addition of endorectal surface coils to conventional MR imaging, spatial resolution is increased and anatomic definition is improved. T2-weighted turbo spin-echo sequences allow the five layers of the rectal wall to be distinguished. Rectal carcinoma in T2-weighted turbo spin-echo sequences gives medium-to-low signal intensity, higher than the muscular layer. MRI and ERUS demonstrate equivalent efficacy in the pre-operative staging of rectal tumours. Overall accuracy rates of 70–90% have been reported for staging of rectal tumours using MRI with endorectal coils. In the evaluation of lymph nodes, MRI does not offer significant improvement in accuracy rates compared with ERUS. It is unlikely, however, that MRI will gain widespread usage because of lack of widespread availability and significantly increased financial costs.

In conclusion, ERUS is currently the best modality available in the pre-operative staging of rectal cancer. Future improvements may include integration with other modalities such as MRI or PET. However, until further improvements are made, the speediest and best tolerated modality is ERUS.

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Predictive Markers in Physiology and Anatomy for Outcomes in Rectal Cancer Patients

Johann Pfeifer

Introduction

In 2004 colorectal carcinoma was the most common malignant tumour in Austria, with about 5000 new patients per year. Furthermore, this tumour was responsible for the second largest number cancer deaths behind lung cancer in men and breast cancer in women. About 50% of all colorectal cancers are situated in the rectum [1]. Due to better surgical techniques, improvement and selection for radio- and/or chemotherapy, the rate of local recurrences could be reduced. The aim of this chapter is to highlight the importance of precise knowledge of anatomy and physiology as well as the critical steps in avoiding pitfalls in rectal cancer surgery.

History

It has been well known for many years that the outcome of colon cancer surgery in the long run is much better than in rectal cancer [2–4]. There have been grounds for the assumption that surgical technique is a major cause for this, for many decades. In the early 1980s, Heald reported a significant decrease of local recurrence rates (<5%) by improving surgical technique, thus challenging the importance of the new, upcoming therapy method of additional post-operative radiotherapy [5]. He stressed the importance of using the total mesorectal excision (TME) in the "holy plane", thus using embryological bloodless planes. In 1995 Hermanek and co-workers of the German Colorectal Cancer Study Group (SGCRC) demonstrated that the surgeon is a prognostic factor in rectal cancer outcome. Surgery is directly related to local recurrence and thus to overall survival [6].

While achievement of adequate proximal and distal margins has been common sense for decades, at about the same time the pathologist Quirke reported on the importance of the possible circumferential margin involvement in rectal cancer. Although the surgeon thought that he did a curative resection, margin-disease-free resection, in 25% circumferential margin involvement could be demonstrated on the pathological specimen leading to a 78% rate of local recurrence [7].

In 2002 Nagtegaal et al. reported that the role of the pathologist is not limited to the microscopic evaluation of the specimen after curative resection but that macroscopic evaluation of the TME specimen will provide feedback to the surgeon with regard to the quality of the operation performed, which may have prognostic significance [8]. A simple classification for the evaluation of the integrity of the mesorectum was proposed (complete, nearly complete and incomplete). In the above-mentioned study in patients with a *negative* circumferential margin the overall recurrence and survival rates were statistically worse in patients with an incomplete TME compared to those with a complete or nearly complete TME (28.6 *vs.* 14.9% and 90.5 *vs.* 76.9%, respectively) [8].

Goals in Rectal Cancer Surgery

Ideal rectal cancer surgery can therefore be summarised as follows:

1. preparation in the right planes
2. no bleeding during and after the surgery
3. no breakdown of the mesorectum
4. adequate margins: proximal, distal, lateral
5. no tension of the anastomosis
6. no functional deficits.

Factors for Success

Although many studies have demonstrated the importance of the concept of TME [5, 9–11], real life is very different. Even in highly specialised rectal cancer surgery studies, where we expect motivated and devoted rectal cancer surgeons, TME was incompletely removed in up to 23.9% [8]. Therefore we have to ask ourselves why this is the case.

In principle there are 3 factors responsible for success or failure:
1. patient-related factors
2. tumour-related factors
3. technical factors.

1. Patient-Related Factors

Most of the patient-related factors cannot be influenced by the surgeon. Due to the anatomically larger extension of the small pelvis in female patients, surgery is in most cases a little easier to perform and therefore results are better [3–6]. As colorectal cancer is a disease of elderly patients, we can count on a substantial number of patients who are unfit for surgery due to age and comorbidities. Although anaesthesia is rarely a contraindication for surgery, a sense of responsibility of the surgeon will sometimes limit a possible curative resection to a palliative procedure (e.g. local excision, stent). Obesity of the patient may influence the choice between conventional or laparoscopic assisted technique [12]. But the latter, if performed, still has a tough learning curve.

2. Tumour-Related Factors

Most colorectal cancers develop from polyps (adenoma–carcinoma sequence). However, other tumours may develop when dysplasia in the mucosa arises, such as in long-standing ulcerative colitis, Crohn's disease, flat adenomatous disease and perhaps in some cases of hereditary non-polyposis colorectal cancer (HNPCC) patients (dysplasia–carcinoma sequence). In praxis, stage and grading of the tumour itself as well as mobility, size and level of the rectal cancer are facts that must be accepted by the surgeon, and they all influence outcome. Newer studies with a multimodal concept including neoadjuvant therapy seem to be promising [13, 14].

3. Technical Factors

Quality of surgery for rectal cancer may be influenced by several more or less technical aspects. We know for example two different kinds of obesity. Some patients have a very thick subcutaneous layer, but inside the peritoneal cavity we see no fatty tissue. Others may have a thick mesentery or fatty appendices epiploicae, all leading to difficulties in anatomical orientation or operation field adjustment problems during surgery. Sometimes important anatomical structures may be non-visible and/or non-palpable. Furthermore, tissue consistency in elderly patients might be very friable, thus creating a surgical challenge.

It should also be mentioned that technical equipment (Ultracision®, Ligasure®), including a good light source (e.g. head set, rectal hook with light source) and a devoted assistant during the operation help to make the operation easier.

Technique in Rectal Cancer Surgery

General Remarks

It should be emphasised that preparation under direct vision as well as sharp dissection is mandatory in rectal cancer surgery. Radical surgery in the pelvis with TME has gained wide acceptance. This technique involves the following steps:
1. above the pelvic rim
2. below the aortic bifurcation
3. along the pelvic side walls
4. distal anterior dissection
5. posterior and distal dissection
6. extreme distal dissection.

1. Above the Pelvic Rim

After packing the small bowel into the upper abdomen, the operation starts with the mobilisation of the left and sigmoid colon by developing the embryonic plane between the mesocolon and the abdominal wall (white line of Toldt). By staying in this plane close to the bowel wall, damage to the gonadal vessels, which can lead to annoying bleeding, can be avoided. In most cases a complete mobilisation of the left colonic flexure is necessary to achieve enough length for a tension-free anastomosis. I prefer an approach from lateral *and* medial (through the lesser sack) to achieve a bloodless dissection of the greater omentum and splenic flexure mobilisation. It should be mentioned that this can also be done nicely with the laparoscopic assisted technique. Technical devices like Ultracision® or Ligasure® are very useful. It seems that if a J-pouch for a better functional outcome is planned, a segment of descending colon should be used rather than the sigmoid colon, which demands extensive left colon mobilisation [15]. Furthermore the sigmoid colon is more prone to colon wall irregularities like diverticular disease. Next the incision of the serosa from the medial (right) side of the left colon should be done continuing upwards to the inferior mesenteric artery, downwards to the pelvis until the cul-de-sac is reached. There is still no proof that high ligation (close to the aorta) of the inferior mesenteric artery is

better than low ligation (after turn off of the left colonic artery) [16]. The inferior mesenteric vein should be divided close to the lower edge of the pancreas. At this point of the operation I prefer to divide the bowel (proximal dissection margin) so as to have good vision and access for the next step.

2. Below the Aortic Bifurcation

Visceral nerves often travel along big vessels. The superior hypogastric plexus in front of the aorta ends when this vessel forms the right and left iliac arteries. The outflow of the superior hypogastric plexus is the right and left hypogastric nerves. It should be mentioned that difficulties in avoiding damage to these structures may occur due to the large variability of these nerves. Careful dissection under the aortic bifurcation in the midline towards the pelvic rim will avoid damage. By proceeding laterally these important nerve structurs can be easily identified.

We always identify the left ureter at the iliac crest, which runs *medial* from the gonadal vein (squeezing). The fascial structures must be obeyed. From the embryological point of view the visceral and somatic "body" merge in the small pelvis and must be identified to do the dissection in the bloodless and oncological correct plane. Stelzner called the visceral body envelopping fascia "Grenzlamelle" [17]. Clinically surgery must be done *between* the "Grenzlamelle" and the fascia pelvis parietalis interna, which covers the muscles of the small pelvis. Inside the small pelvis the visceral nerves (sympathetic Plexus hypogastricus, parasympathetic Plexus pelvicus) are situated, the somatic structures Plexus pudendalis – pudendal nerve lies under the fascia pelvis parietalis interna travelling to the muscles of the pelvic floor using Alcock's canal to reach the external anal sphincter complex.

3. Along the Pelvic Side Walls

In the upper part with the hypogastric nerves in view, the presacral (retrorectal) space is entered. Then the dissection is carried out further laterally and downwards. It should be mentioned that more distally the pelvic splanchnic nerves (*N. erigentes*) join the hypogastric nerve and form the inferior hypogastric plexus. The lateral ligaments (stalks) which contain also the accessory middle rectal vessels seem to be adhered between the mesorectum and the nerve plexus. The vessels are often very small and can be divided easily with electrocautery. Alternatively, the ligaments are clamped, divided and ligated. Good tension/countertension of the specimen and a good light source to visualise the border of the mesorectum are always important to avoid inadvertent bleeding.

4. Distal Anterior Dissection

In male patients, the peritoneum is incised at the retrovesical reflection. Then the mobilisation is continued in the plane between the seminal vesicles and more distally the prostate and Denonvilliers' fascia. In contrast with rectal dissection for benign disease, Denonvilliers' fascia should not be divided.

In women the transverse incision is made anterior to the rectovaginal reflection. Then the plane between the rectum and vagina is developed until the pubis can be felt anteriorly. In praxis this part of dissection is often more difficult in women than in male patients. Bleeding (especially from the postvaginal venous plexus) is controlled by electrocautery.

Even nowadays sometimes there might be problems in identifying the Denonvilliers' fascia. Recently, in a histological study, Lindsey et al. reported that in rectal cancer patients the surgeons are more prone to dissect close to the bowel wall, leaving the Denonvilliers' fascia anteriorly (on the posterior wall of the prostate) [18].

5. Posterior and Distal Dissection

The rectal dissection on the posterior side starts just above the promontory. Leaving the hypogastric nerves aside, the presacral space is entered. In the correct plane we expect minimal bleeding. At the S3 or S4 level, we see the retrosacral fascia (Waldeyer). This structure varies from a thin layer to a thick ligament. It is important to sharply cut this structure by turning the scissors or electrocautery now *parallel* to the pelvic floor. If downwards dissection is to be carried out, the presacral venous plexus may be injured, which can lead to life-threatening bleeding. Once Waldeyer's fascia is cut, the tip of the coccyx is reached. Nowadays a 2-cm distal margin is acceptable, but coning of the mesorectum must be avoided.

6. Extreme Distal Dissection

For the most distal part of the rectum I prefer step by step circular preparation along the muscle tube. At the very end of the rectum it is easy to staple the stump with a 30-mm stapling device as at this point no mesorectum is present. We have to bear in mind that the holy plane of perimesorectal dissection ends in the interspincteric plane.

Physiology: Markers for Quality of Life

Besides oncologic correct dissection of the rectal cancer, the surgeon also has a responsibility to provide a good physiologic outcome. In praxis, markers for quality of life are as follows:

1. preservation of continence
2. reasonable bowel frequency
3. avoidance of permanent sexual and urinary disturbances.

1. Preservation of Continence

Although avoiding a permanent stoma is often taken *sine qua non* for a good outcome after rectal cancer surgery, functional success must be considered separately. Functional disturbances after low anterior resection (LAR) like frequency of bowel action, diarrhoea, faecal incontinence and even constipation have been reported [19, 20]. Low colorectal or coloanal anastomoses especially are associated with worse functional results than a high anterior resection [21]. Thus it is important to evaluate the sphincter function to avoid permanent faecal incontinence, as a sphincter-sparing operation in a patient with poor sphincter function does not make sense [22].

On the other hand, it must be made clear that in a patient with a very low anastomosis, the risk of an anastomotic insufficiency is high. To avoid late postoperative problems (e.g. urgency, frequent evacuations etc.) we therefore suggest in these cases the liberal creation of a temporary stoma [23].

2. Reasonable Bowel Frequency

It is well known that straight end–end anastomosis and thereby loosening of a reservoir may lead to frequent evacuations, especially in the first 2 years till adaptation of the "new rectum" and regaining of some reservoir capacity has occurred. Therefore construction of a colonic pouch, which should be smaller in size (5–6 cm in length) than small bowel pouches like in ulcerative colitis or familial adenomatous polyposis (FAP) surgery, has been proposed [24]. Advantages of pouches are less frequent bowel movements, decreased clustering of stools and possibly lower risk of anastomotic leakage. However, due to the especially narrow pelvis in male patients, from an anatomical point of view, a colon pouch is not always possible. In a recent study, coloplasty was recommended as it was possible in every case, compared to colon J-pouch, which could be constructed in only 75% [25]. Furthermore, it seems that besides a better rectal sensitivity, coloplasty provides similar functional results to the J-pouch [25]. Another option is a simple side-to-end anastomosis.

3. Avoidance of Permanent Sexual and Urinary Disturbances

Good surgical technique is necessary to avoid nerve damage leading to sexual dysfunction or urinary incontinence problems. The critical steps are at the pelvic rim, where the dissection is between the hypogastric nerves to the lateral and mesorectum and by dissection far down in the pelvis. When identifying the Denonvilliers' fascia, the surgeon must be aware that just lateral of it near the back side of prostate, the nerve bundles responsible for adequate bladder and sexual function may easily be injured. In rectal carcinomas, which are situated very deep and on the anterior wall, damage to this nerve structure can rarely be avoided. Routine use of the nerve stimulator Cavermap® as a guidance tool has been recently proposed [26]. Extended lymphadenectomy as described by Koyama et al. in 1984 leads to a better survival rate (18% overall, 36% in Dukes C), with the price of urinary dysfunction in 39 *vs*. 9% and impotency 76 *vs*. 28% [27]. Therefore, today we cannot recommend this approach.

Evidence for Surgeon Variability

Resection rates of cancers vary considerably from centre to centre; local recurrence rates range from 2.6 to 42% [3–5, 28]. Survival rates also vary considerably in some series from centre to centre and from surgeon to surgeon. The disease stage breakdown of different series of patients may vary considerably and might account for some of the differences. However, patient mix cannot account for the very wide differences noted between some series.

Case Volume

Porter et al. compared the results of colorectal-trained and general surgeons as well as high-volume and low-volume surgeons in regards to abdom inoperineal resection (APR) and LAR [29]. The study reviewed 683 resections carried out by a total of 52 surgeons over a 7-year period. Low-volume surgeons (less than 3 cases per year) accounted for 47% of the cases, whereas high-volume surgeons (greater than or equal to 3 cases per year) did the rest of the cases. In 34% a colorectal specialist took care of the patients; the rest was done by general surgeons. Regarding the operations performed, the percentage of APRs for the

specialists was 28% whereas it was 47% for the general surgeons; LAR was carried out by the colorectal surgeons in 73% and in 35% of the cases done by the general surgeons. Analysis of the long-term results suggests that both specialty training *and* volume of cases had an impact on the local recurrence and survival rates. The local recurrence rates for each subgroup of surgeons are as follows: high-volume colorectal surgeon, 10.4%; low-volume colorectal surgeon, 21.1%; high-volume general surgeon, 27.8%; and low-volume general surgeon, 44.6%. The corresponding survival rates are as follows: high-volume colorectal surgeon, 67.3%; low-volume colorectal surgeon, 54.5%; high-volume general surgeon, 49%; and low-volume general surgeon, 39%.

Read et al. retrospectively compared the results of colorectal surgeons and general surgeons that carried out proctectomy on a population of 384 rectal cancer patients that all underwent neoadjuvant radiotherapy [30]. The colorectal surgeons did 65% of the cases, the general surgeons 35%. The disease-free survival was 77% for the specialists and 68% for the general surgeons ($p<0.05$). The local recurrence rates were 7% for the colorectal surgeons and 16% for the generalists ($p<0.05$). The rate of LAR was also significantly higher in patients operated on by the colorectal surgeons (52 *vs*. 30%).

Martling et al. reviewed the Swedish rectal cancer resection results after a series of surgical TME workshops that were held in Stockholm in the 1990s by Bill Heald [11]. Over a 2-year period (1995–1997), 652 rectal cancer patients were operated on. High volume surgeons (13 or more resections per year) did 48% of the cases. The local recurrence rates were significantly lower for the high-volume surgeons (4%) than for the low-volume group (10%, $p=0.02$); the same was true for the survival rates (89 *vs*. 82%, $p=0.007$).

Specialisation and Colorectal Unit

Garcia-Granero et al. examined the results of 94 patients operated on by 14 general surgeons in a university general surgery department to the outcomes of 108 patients operated on by only 4 surgeons once a specialised colorectal unit had been formed [31]. The colorectal unit's rate of performing APRs dropped significantly. Likewise the rate of pelvic recurrence was 11% for the unit as opposed to 25% for the general surgery unit.

Smedh et al., in a similar comparison of rectal resection results of a recently formed specialised unit (144 patients) to the prior results of a larger group of surgeons (133 patients), reported the peri-operative results [32]. Regarding the colorectal unit's results, the post-operative mortality rate decreased from 8 to 1%, the overall post-operative complication rate dropped from 57 to 24%, the re-operation rate fell from 11 to 4% ($p<0.05$), and the length of stay dropped from 13 to 9 days.

Conclusions

Every rectal cancer patient is a challenge for the surgeon. Good knowledge of the anatomy and physiology is the prerequisite for a successful outcome. Well educated and trained colorectal surgeons provide better results concerning local recurrence and overall survival. The impact of specialisation is more important than case volume. Furthermore, colorectal specialists perform more sphincter-saving operations for rectal cancer.

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Rectal Cancer: Pathological Features and their Relationship to Prognosis and Treatment

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Introduction

Rectal carcinoma represents 35–40% of colorectal cancers [1]. Colorectal carcinoma is one of the most common tumours in developed countries and is the third in terms of frequency. It is the second most common cause of death from neoplasia. In Italy around 20 000–30 000 new cases of rectal cancer are observed each year. The 5-year survival rates are around 50–60%, depending on the stage of the disease. Rectal carcinoma has a very good prognosis when confined to the wall of the rectum, while poor prognosis is associated with extension beyond the wall and lymph node metastasis [2]. Patients with residual tumour (R) have poor survival rates; patients with microscopic residual tumour (R1) have a slightly better prognosis than those with macroscopic residual tumour (R2). R1 patients are generally associated with locoregional disease while R2 patients have distant metastases [3].

The outcome depends essentially on early diagnosis. Colorectal carcinoma arises, in the majority of cases, from macroscopically assessable precancerous lesions, namely adenomatous polyps [4]. Genetic studies have characterised the molecular basis of the adenoma–carcinoma sequence.

About 75% of new cases of colorectal carcinoma are observed in patients with no obvious risk factors, while 25% of patients are associated with high-risk categories. The latter include hereditary conditions (up to 5% of colorectal carcinomas) such as familial adenomatous polyposis coli (FAP) and hereditary non-polyposis colorectal cancer (HNPCC).

Pathogenesis

The molecular pathways of colorectal carcinoma are very well known.

Sporadic adenocarcinoma follows one of two molecular pathways:

(1) Most cases present a well defined sequence of genetic alterations accumulated during neoplastic progression that involve the APC, Ki-Ras, p53, MCC and DCC genes as well as partial deletions of chromosomes 5, 17 and 18. Neoplastic progression has its morphological manifestation in the adenoma–carcinoma sequence. Inactivation of the suppressor gene APC is, in most tumours, the earliest event that influences the subsequent ones [5–9].

(2) Around 10–15% of carcinomas present an early primary event, namely inactivation of mismatch repair genes (e.g., mutator genes: hMSH2, hMSH1, hPMS1, hPMS2). Morphologically this alternative pathway is manifested in epithelial hyperplasia and a serrated pattern. These carcinomas, once defined as RER-positive (Replication ERror), are characterised by widespread mutations in the genome, easily identified by the analysis of repeated sequences of 1–4 bases (microsatellite) that are particularly subject to insertions or deletions [10–13]. They are currently referred to as carcinomas with microsatellite instability and are characterised by extensive nucleotide insertions or deletions in numerous, intrinsically unstable repeated sequences in tumour DNA, termed microsatellite. A change in the length of these sequences, located within or near genes involved in cellular proliferation, can alter the quality or quantity of different gene products. Mutation in a target gene such as a proto-oncogene or a tumour suppressor gene will have a defined role in tumour progression. Microsatellite instability is caused by alteration of the DNA mismatch repair genes. MSI cancers are subdivided into high-frequency microsatellite instability (MSI-H) and low frequency microsatellite instability (MSI-L) [14].

In cancers from other gastrointestinal sites, MSI tumours show a low frequency of p53 mutations, less lymph node involvement and a better prognosis [8, 12]; they also show a higher risk of multiple neoplasia [15]. From a morphologic point of view, MSI-H carcinomas show distinctive features: they are generally located in the proximal colon, show high grades and are more frequently mucinous, medullary or undifferentiated carcinomas with a marked “Crohn like” inflammatory infiltrate, and a high number of

intraepithelial lymphocytes. Except for the medullary type, they do not show distinctive histological features and their phenotype must be determined by genetic studies (microsatellite analysis by PCR) or immunohistochemical techniques (MLH1 and MSH2 staining).

MSI-H tumours are characteristic of HNPCC, originating from a germline mutation in a DNA mismatch repair gene followed by somatic inactivation of the second allele. In the majority of sporadic adenocarcinomas microsatellite instability originates from inactivation of hMLH1 gene by promoter hypermethylation [12, 16].

FAP and HNPCC are autosomal dominant disorders [7]. The former is caused by a mutation of the APC gene on the long arm of chromosome 5, while the latter originates from a germline mutation in a DNA mismatch repair gene.

The outcome of rectal cancer is related to stage of disease at time of diagnosis and to the presence of local recurrences with disease progression no longer responsive to therapy [17].

Local recurrences are the primary cause of death and are related to lymph node metastasis, depth of invasion through the wall and involvement of the circumferential (radial) margin. Treatment of colorectal carcinoma has changed dramatically over the last 30 years due to improved information, better surgical techniques and new therapeutic strategies. Surgical resection remains the treatment of choice for stage I disease, but locally advanced neoplasia may also involve new therapeutic options like radiotherapy, chemotherapy and hyperthermia. These therapies are now used as neoadjuvant therapies in advanced colorectal cancer in order to reduce the tumour stage. This will increase the resectability of the tumours, provide a possibility to preserve the anal sphincter and achieve a reduction in local recurrences [18, 19]. These new therapies also change the pathologic evaluation.

Pathological Evaluation of Rectal Cancer

Surgical resection remains the most effective therapy for colorectal carcinoma, and the best estimation of prognosis is related to the pathologic findings on the resected specimen [20]. These parameters are best evaluated by a standardised sampling and by a standard pathology report or checklist [21–23] (Table 1). The pathologic report should provide all the relevant information needed to assess the stage of disease including grade, extent of invasion, presence of extramural vascular invasion, configuration of tumour borders and the presence of a peritumoral lymphocytic response (Table 2). Microscopic assessment of margins and lymph nodes must also be included [3, 22].

Primary Tumour

Histologic Types (WHO Classification 2000) [24]

Adenocarcinoma

Epithelial tumour composed of glands. It is the most frequent histotype. Adenocarcinomas are then subdivided depending on differentiation.

Mucinous Adenocarcinoma (Colloid)

More than 50% of the lesion is composed of pools of extracellular mucin that contains malignant epithelium as a strip of cells or single cells. Many MSI+ carcinomas are of this histopathological type.

The prognosis of this tumour type is still controversial [25–27].

Adenosquamous Carcinoma

An unusual tumour that shows features of both squamous carcinoma and adenocarcinoma, either as separate areas within the tumour or admixed. Squamous carcinoma is very rare.

Medullary Carcinoma

This rare variant is characterised by sheets of uniform malignant cells with vesicular nuclei, prominent nucleoli and an abundant pink cytoplasm exhibiting solid growth and prominent infiltration by intraepithelial lymphocytes. It has a favourable prognosis when compared to other poorly differentiated and undifferentiated colorectal carcinomas. It is always associated with the MSI+ phenotype [25, 28, 29]. It can be sporadic [28] or associated with HNPCC [29].

Signet-Ring Cell Carcinoma

It is defined by the presence of more than 50% of tumour cells with prominent intracytoplasmic mucin [30]. The typical signet-ring cell has a large mucin vacuole that fills the cytoplasm and displaces the nucleus. Some MSI+ tumours belong to this histotype.

Table 1. Rectal resection: checklist

Clinical information	Relevant history	Previous colon adenoma(s)/carcinoma(s)
		Familial adenomatous polyposis syndrome Hereditary non-polyposis colon cancer syndrome Familial hamartomatous polyposis syndrome Inflammatory bowel disease
	Relevant findings	
	Clinical diagnosis	Colonoscopic endoscopic ultrasound and/or imaging studies
	Procedure	
	Operative findings	Low anterior resection, abdominoperineal resection
	Anatomic site(s) of specimen(s)	Rectosigmoid, rectum and anal canal
Macroscopic examination	Specimen	Organ(s)/tissue(s) included Unfixed/fixed Number of pieces Dimensions Appearance of mesorectal envelope Results of intraoperative consultation
	Tumour	Location Configuration Dimensions Descriptive characteristics (e.g., colour, consistency) Ulceration/perforation Distance from margins (proximal, distal, circumferential) Appearance of serosa overlying tumour Estimated depth of invasion Lesions in no cancerous rectum (e.g., proctitis, other polyps) Regional lymph nodes Metastasis to other organ(s) or structure(s) Rectum uninvolved by tumour Other tissue(s)/organ(s)
	Tissues submitted for microscopic evaluation	Carcinoma Points of deepest penetration Interface with adjacent sigmoid colon/anal canal Visceral serosa overlying tumour Margin (proximal, distal, circumferential) All lymph nodes Other lesions (proctitis, polyps) Frozen section tissue fragment(s)
Microscopic evaluation	Tumour	Histologic type Histologic grade Extent of invasion Blood/lymphatic vessel invasion Perineural invasion Extramural venous invasion Peritumoral lymphocytic response Pattern of growth at tumour periphery (infiltrating border, pushing border) Associated perirectal abscess formation, if present Associated pneumatosis intestinalis, if present
	Margins	Proximal Distal Circumferential (specify distance of carcinoma from closest circumferential margin)
	Regional lymph nodes	Number Number involved by tumour
		Inflammatory bowel disease
	Additional pathologic findings, if present	Dysplasia Adenomas Other types of polyps
	Distant metastasis (specify site)	Other tissue(s)/organ(s)
	Results/status of special studies (specify)	
	Comments	Correlation with intraoperative consultation Correlation with other specimens Correlation with clinical information

Table 2. pTNM: pathologic staging

pT: primary tumour, not treated
- **pTX:** cannot be asessed
- **pT0:** no evidence of primary tumour
- **pTis:** carcinoma *in situ*, intraepithelial or intramucous
- **pT1:** tumour invades submucosa
- **pT2:** tumour invades muscularis propria
- **pT3:** tumour invades through the muscularis propria into the subserosa or the non-peritonealised perirectal soft tissue; the infiltration is evaluated in mm beyond the border of the muscularis propria
  - pT3a: minimal invasion: less than 1 mm
  - pT3b: slight invasion: 1–5 mm
  - pT3c: moderate invasion: >5–15 mm
  - pT3d: moderate invasion: >15 mm
- **pT4**: tumour directly invades other organs or structures (T4a) and penetrates visceral peritoneum (T4b)

Tumours that invade the external sphincter are classified as T3 while tumours that invade the musculus levator ani are classified as T4

pN: regional lymph nodes
- **pNX:** cannot be assessed
- **pN0:** no regional lymph node metastasis
- **pN1:** metastasis in 1 to 3 regional lymph node
- **pN2:** metastasis in 4 or more regional lymph nodes

pM: distant metastasis
- **pMx:** cannot be assessed
- **pM0:** no distant metastasis
- **pM1:** distant metastasis

After pre-operative therapy pTNM categories should have the prefix "Y"

Undifferentiated Carcinoma

These tumours lack morphological evidence of differentiation. They are typically associated with microsatellite instability.

Small Cell Carcinoma

Rare and aggressive tumour. Patients usually have liver and lymph node metastasis at diagnosis. These neoplasia show neuroendocrine differentiation [31].

Adenocarcinoma represent 85% of cases, mucinous represent 10% and the other histotypes 5%.

Histologic Grade

Based on Jass' criteria, adenocarcinomas are subdivided into:
- Well differentiated: made of simple or complex regular glands that preserve nuclear polarity and show nuclei of uniform dimensions (Fig. 1a).
- Moderately differentiated: made of simple or complex, regular or slightly irregular glands with alteration or absence of nuclear polarity (Fig. 1b).
- Poorly differentiated: made of highly irregular glands with loss of nuclear polarity or no gland formation (Fig. 1c).

Multivariate analysis has shown that histologic grade is a prognostic factor independent of stage [20, 26, 32].

To reduce the degree of interobserver variability in the grading of colorectal cancer a 2-tiered system has been proposed. This system is relatively easy and reproducible and is based solely on the presence of glands [25]:

Low-grade carcinoma: greater than or equal to 50% gland formation.

High-grade carcinoma: less than 50% gland formation.

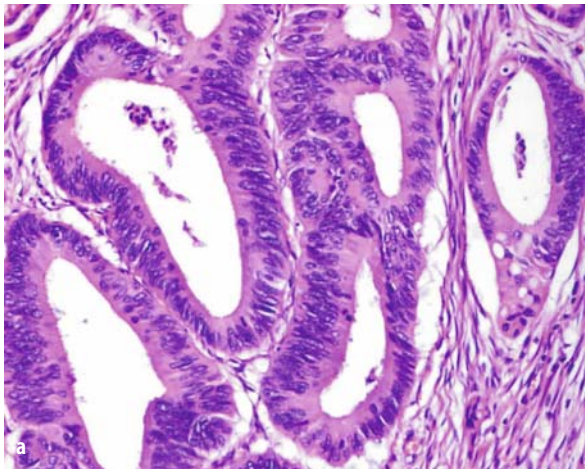
Signet-ring cell carcinoma, small cell carcinoma and undifferentiated carcinoma are considered high grade. Signet-ring cell and small cell carcinoma have shown a poor prognosis that is independent of stage [26].

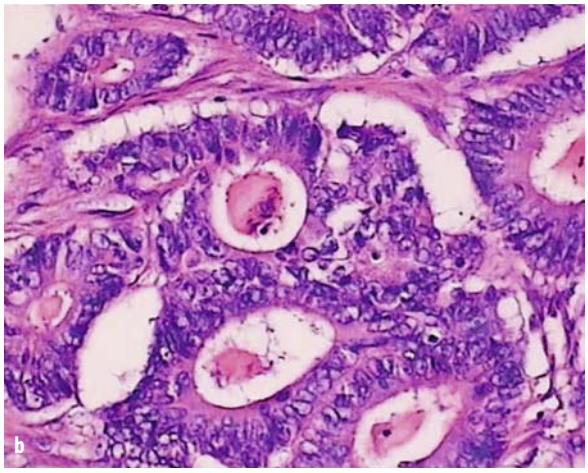
Extent of Invasion

The diagnosis of adenocarcinoma is made when there is involvement of the muscularis mucosae with invasion of the submucosa. Lesions morphologically resembling adenocarcinoma but confined within the glandular basement membrane (carcinoma *in situ*) or infiltrating the lamina propria (intramucosal carcinoma) have almost no metastatic potential. For these lesions the term "intraepithelial neoplasia" should be used.

Full thickness muscular invasion with extramural extension has been reported to influence prognosis (Fig. 2a, b): an extramural extension greater than 5 mm has been shown to be the critical point associated with adverse outcome in most studies [33].

Serosal penetration has been demonstrated to be an independent prognostic variable with a strong negative impact on prognosis (Fig. 2c) [33, 34]. It has been shown that the frequency of distant metastases is higher in cases with perforation of the visceral peritoneum compared to cases with direct invasion of adjacent organs or structures without perforation of the visceral peritoneum (occurring in about 50% and 30% of cases, respectively). Furthermore, the median survival time following surgical curative resections has been shown to be shorter. Shepherd has suggested that the prognostic power of local peritoneal involvement in curative resections may supersede that of either local extent of tumour or regional lymph node status [34].





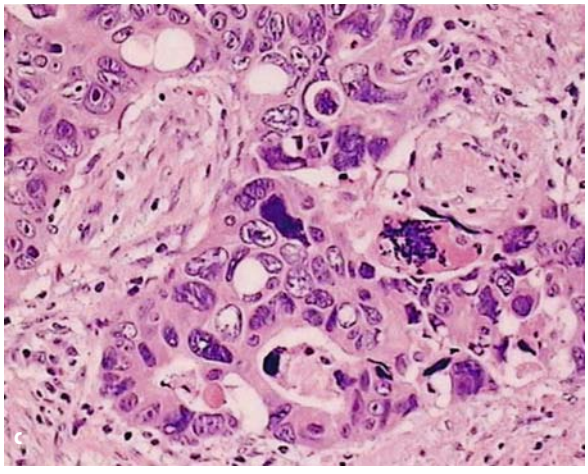
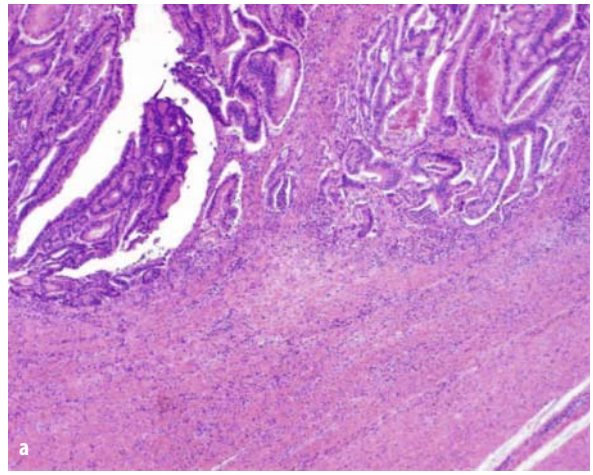
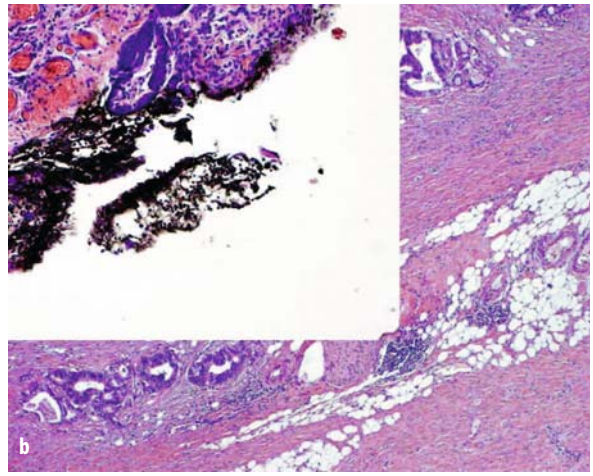


Fig. 1a-c. Adenocarcinoma histologic grade. **a** Adenocarcinoma well differentiated. **b** Adenocarcinoma moderately differentiated. **c** Adenocarcinoma poorly differentiated





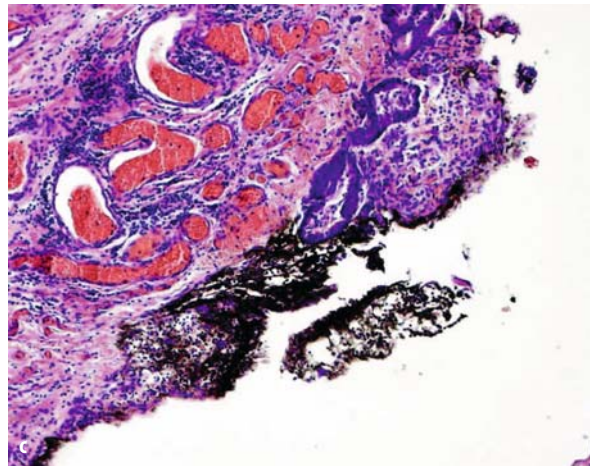


Fig. 2a-c. Extent of invasion. **a** Intramural extension. **b** Extramural extension. **c** Serosal invasion

Venous Invasion

Extramural venous invasion (Fig. 3) has been demonstrated as an independent prognostic factor [32, 35, 36] that correlates with a higher rate of liver metastasis [36, 37]. The significance of intramural venous invasion is less clear, although this parameter should be reported in the diagnosis [25, 36].

Lymphatic (Thin-Walled) Vessel Invasion and Perineural Invasion

In several studies, both lymphatic invasion and perineural invasion have been shown by multivariate analysis to be independent indicators of poor prognosis [32, 35, 38–40]. The prognostic significance, if any, of the anatomic location of these structures is not defined. Furthermore, it is not always possible to distinguish lymphatic vessels from postcapillary venules, as both are small, thin-walled structures. Thus, the presence or absence of tumour invasion of small, thin-walled vessels should be reported in all cases and its anatomic location within the colonic wall noted [25].

Tumour Periphery: Growth Pattern

The growth pattern at the advancing edge of the tumour [41] has been shown to have prognostic significance independent of stage and may predict liver metastasis [42, 43].

1) Pushing borders: the advancing edge of the tumour is regular, well demarcated or only slightly irregular.
2) Infiltrating borders: by either "streaming dissection" of muscularis propria or dissection of adipose tissue by small glands or irregular clusters of cells, most often in perivascular of perineural areas.

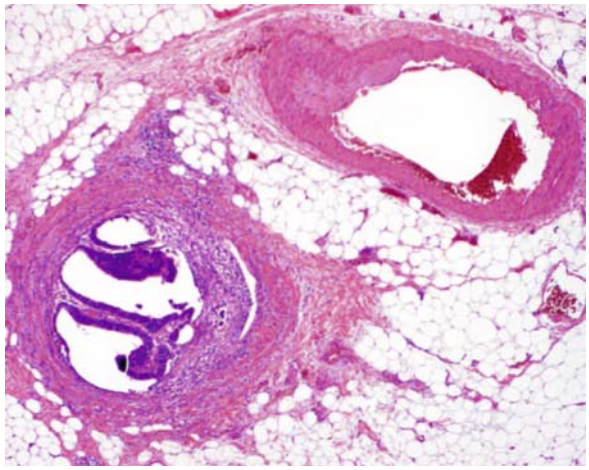


Fig. 3. Extramural venous invasion with neoplastic thrombosis

Infiltrative borders are associated with a poorer prognosis [41].

Some studies, however, revealed problems with the reproducibility of Jass' grading system based on the nature of the advancing tumour margin, which divided rectal tumours into expanding type and infiltrative type [44, 45]. Several investigators have highlighted the histological phenomenon that represents the first step in invasion and metastasis, using the term tumour "budding" [46, 47]. Tumour "budding" is defined as an isolated single cancer cell and a cluster composed of fewer than five cancer cells, observed in the stroma of the actively invasive frontal region. Tumour "budding" intensity (<10; ≥10) has a strong correlation with the pathological characteristics that define tumour aggressiveness. Ueno et al. [48] have demonstrated that patients with expanding

Table 3. Macroscopic pathologic assessment of the completeness of the mesorectum

Incomplete	Little bulk to the mesorectum Defects in the mesorectum down to the muscularis propria After transverse sectioning, the circumferential margin appears very irregular
Nearly complete	Moderate bulk to the mesorectum Irregularity of the mesorectal surface with defect greater than 5 mm, but none extending to the muscularis propria No area of visibility of the muscularis propria except at the insertion site of the elevator ani muscles
Complete	Intact bulk mesorectum with a smooth surface Only minor irregularities of the mesorectal surface No surface defects greater than 5 mm in depth No coning towards the distal margin of the specimen After transverse sectioning, the circumferential margin appears smooth

tumours (Jass' criteria) that had a tumour "budding" intensity ≥10 showed much poorer survival than patients with expanding tumours that had a "budding" intensity <10. In the same way, patients belonging to the infiltrating group by Jass' criteria could be divided into two groups with different outcomes based on the intensity of tumour "budding". Multivariate analysis selected tumour "budding" as a significant independent variable, together with number of nodes involved, extramural spread, lymphocyte infiltration, apical nodal involvement and tumour differentiation. The evaluation of tumour "budding" could improve the grading system with particular reference to potential aggressiveness as a marker of prognostic significance and furthermore is simple and reproducible [48].

Lymphocytic Response to Tumour (at the Leading Edge of Invasive Tumour)

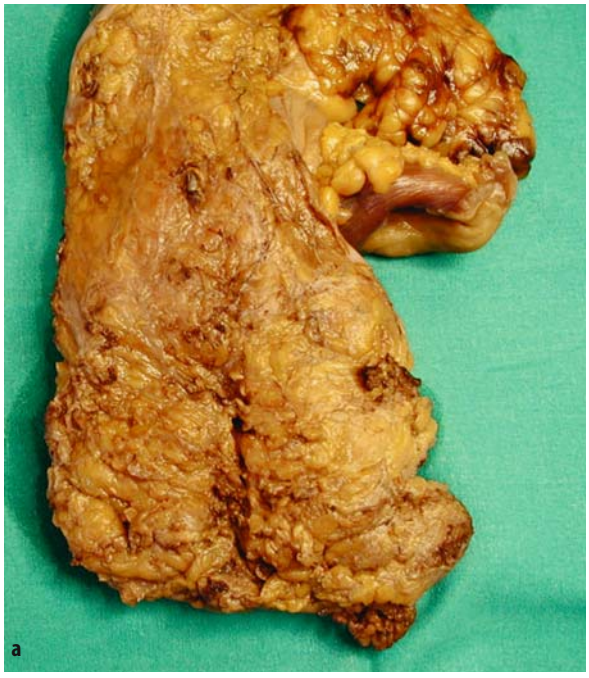
- "Crohn like" lymphocytic infiltrate
- Conspicuous: numerous, big lymphoid aggregates, often with germinal centres, at the periphery of the tumour, located at the external border of muscularis propria.
- Mild: occasional small lymphoid aggregates without germinal centres.
- Absent: rare, small lymphoid aggregates or none.

The presence of a lymphoid reaction has been shown to be a favourable prognostic factor [41, 49, 50]. The presence of a lymphoid reaction at the leading edge of invasive tumour must be distinguished from an intratumoral lymphocytic infiltrate, which is closely associated with microsatellite instability and medullary architecture.

Resection Margins

Status of proximal, distal and radial margins and their distance from the invasive carcinoma must be specified. The circumferential (radial or lateral) margin is the most critical for rectal tumours, because of the high risk of local recurrences. In terms of survival: a positive margin increases the risk of local recurrence 3.5-fold and doubles the risk of death from disease [51]. This margin represents the adventitial soft tissue margin resected by surgery. Careful routine assessment of the non-peritonealised surfaces of the "fresh" specimen throughout its entire length is needed to assess the completeness of mesorectal resection. Macroscopic pathologic assessment of the completeness of the mesorectum of the specimen accurately predicts both local recurrences and distant metastasis [52] (Table 3) (Fig. 4). Mesorectal resection can be scored as complete, partially complete or incomplete [53]. Microscopic evaluation of the radial margin may be difficult on histologic sections and it may be helpful to mark the surface with ink before formalin fixation [25] (Figs. 5, 6).

Routine assessment of the distance between the tumour and nearest radial margin (i.e., "surgical



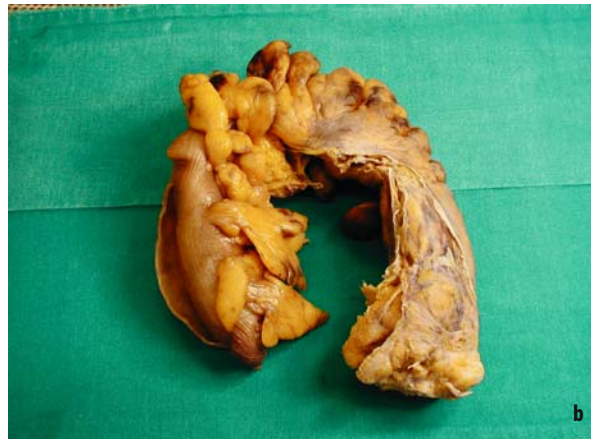


Fig. 4a, b. Macroscopic assessment of the completeness of the mesorectum. **a** Nearly complete. Irregularity of the surface of mesorectal envelope (fresh specimen). **b** Complete. Only minor irregularities of the surface of mesorectal envelope (smooth surface) (fresh specimen)

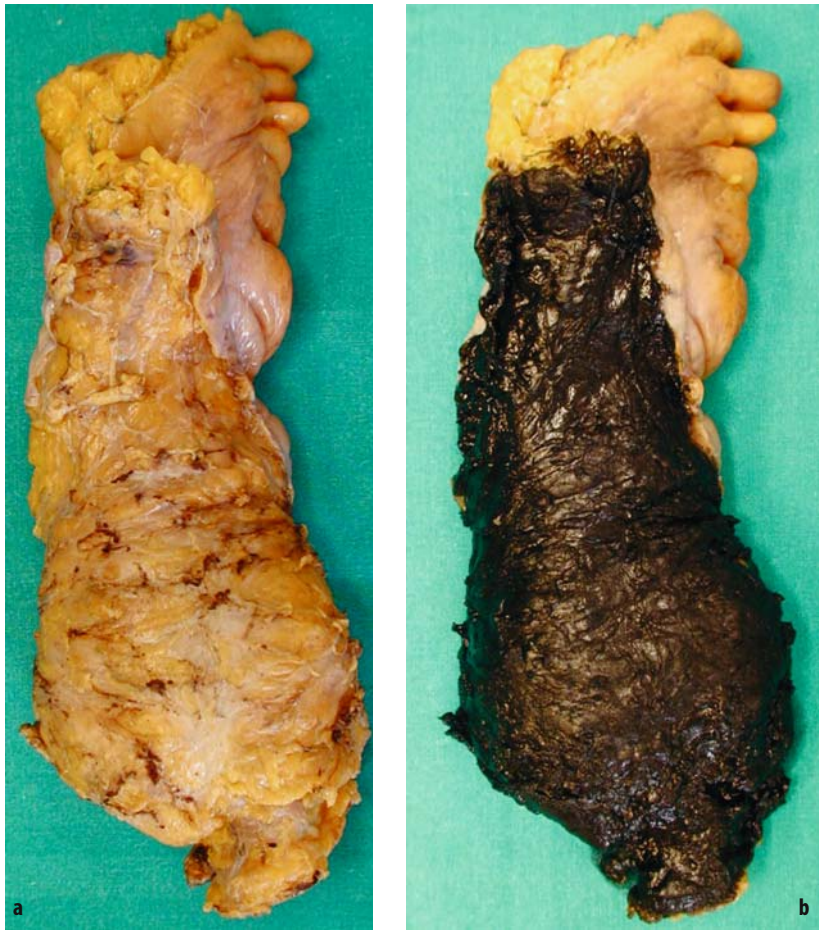


Fig. 5a, b. Mesorectal envelope. **a** Non-peritonealised back surface. **b** Margin marked with ink

clearance") is mandatory [21]. The circumferential margin is scored as positive if the tumour is located 1 mm or less from the inked non-peritonealised surface of the specimen [25] (Fig. 7). This includes tumour within a lymph node as well as direct tumour extension (if positivity is based solely on intranodal tumour, this should be stated). The distance (in mm) of the tumour from the margins, should be present in the pathologic report as it helps to assess the adequacy of surgical resection and identifies patients for adjuvant therapy [54–56].

The quality of the surgical technique is a key factor in the success of surgical treatment for rectal cancer, both in the prevention of local recurrence and in long-term survival. Total mesorectal excision (TME) improves local recurrence rates and corresponding survival by as much 20%. This surgical technique entails precise sharp dissection within the areolar plane outside (lateral to) the visceral mesorectal fascia in order to remove the rectum. This plane encases the rectum, its mesentery, and all regional nodes. High-quality TME surgery reduces local recurrence from 20 to 30%, 8 to 10% or less, and increases 5-year survival from 48 to 68% [57–61].

Moreover, the distance of the tumour from *proximal and distant margins* should also be assessed in millimetres: these measurements represent disease-free colon segments. A positive longitudinal margin, usually the distal one, is considered to be a negative prognostic factor: this margin should be evaluated on the fresh specimen to avoid retraction due to fixation. A macroscopic evaluation is possible because colorectal carcinomas rarely have an intramural spread beyond the macroscopic margins. Anastomotic recurrences are rare when distance of the tumour from these margins is greater than or equal to 5 cm. For neoplasia of the lower rectum treated by low anterior resection, a 2-cm margin is considered adequate [62].

There is a special system to describe tumour remaining in a patient after therapy with curative intent, namely R classification (Table 4). For the surgeon, the R classification indicates the assumed status of the completeness of a surgical excision; for the

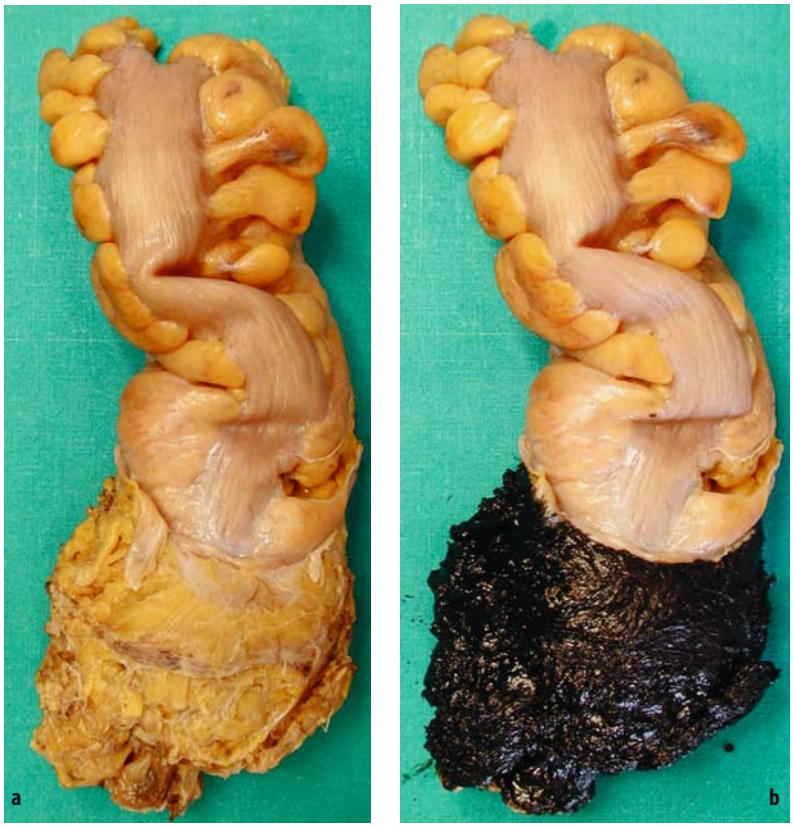


Fig. 6a, b. Mesorectal envelope. **a** Non-peritonealised front surface. **b** Margin marked with ink

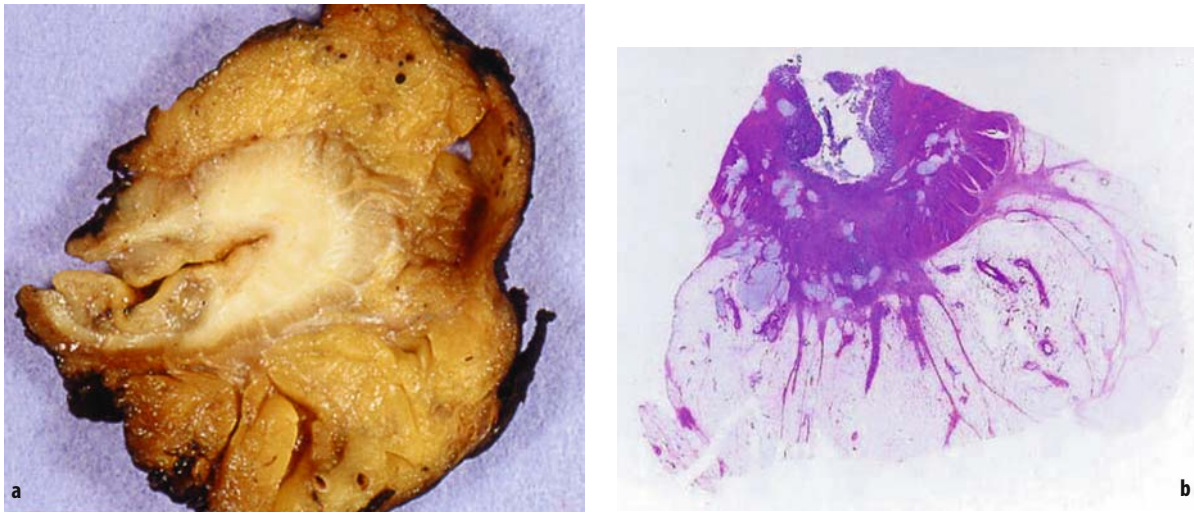


Fig. 7a, b. Radial margin of rectal cancer. **a** Cross-section through the bowel and radial margin: fresh specimen. **b** Tumour is not present in the radial margin

Table 4. R classification: residual tumour

Rx: presence of residual tumour cannot be assessed
R0: no residual tumour
R1: microscopic residual tumour
R2: macroscopic residual tumour

pathologist it is relevant to the status of the margins of a surgically resected specimen. The completeness of resection is dependent in large part on the radial margin. R0 suggests complete tumour resection with all margins negative, R1 is an incomplete tumour resection with microscopic involvement of a margin and R2 is an incomplete tumour resection with macroscopic involvement of a margin and gross residual tumour that was not resected.

Regional Lymph Nodes

The number of lymph nodes evaluated and the number involved by metastasis should always be stated in the pathologic report. Around 7–14 lymph nodes should be evaluated for radical resection, as it has been shown that a lower number does not predict for negativity [3]. If fewer than 12 nodes are found, additional methods (i.e., visual enhancement techniques) should be considered [25]. A smaller number of nodes is acceptable for palliative resection or after neoadjuvant radiotherapy.

Tumour nodules in the perirectal fat without histologic evidence of residual lymph node involvement have two different possibilities. They are classified as metastasis (in the N category as lymph node replacement by tumour) if the nodule has the form and smooth contour of a lymph node (Fig. 8a). If the nodule has an irregular contour, it should be considered as an expression of vascular invasion either microscopic (V1) (Fig. 8b) or macroscopic (V2).

Micrometastases (tumour measuring greater than 0.2 mm but less than or equal to 2.0 mm in the greatest dimension) are classified as N1. The report should specify that it is an N1 (mic) or M1 (mic) micrometastases [25].

The biologic significance of *isolated tumour cells within nodes* (defined as single tumour cells or small clusters of tumour cells measuring 0.2 mm or less) isolated by immunohistochemical or molecular techniques is still not clear. Isolated tumour cells should be classified as N0 [33].

Twelve lymph nodes is still considered the minimal number, but recent studies have shown [63] that no precise value correlates to an accurate staging; the possibility of finding a positive node simply increases with the number of nodes evaluated [64].

Routine assessment of regional lymph node metastasis is limited to the use of conventional pathologic techniques (gross assessment and histologic examination). Current data are not sufficient to use special/ancillary techniques (such as immunohistochemistry, flow cytometry, polymerase chain reaction) to detect micrometastases or isolated tumour cells [25].

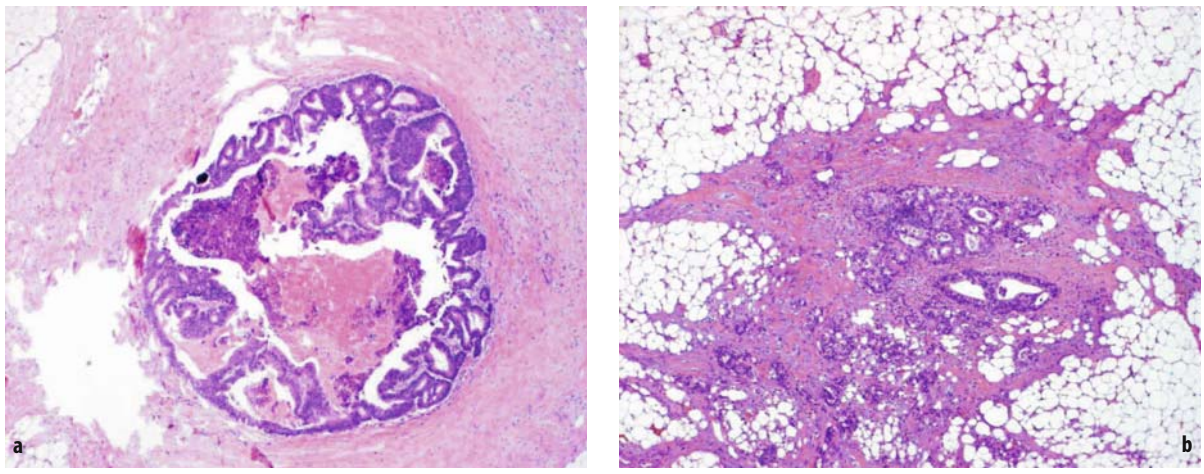


Fig. 8a, b. Tumour nodules in perirectal fat. **a** Nodules with smooth contour: lymph node metastasis. **b** Nodules with irregular contour: vascular invasion (V1)

Non-Regional Lymph Nodes

Metastasis to non-regional lymph nodes is classified as distant metastasis (M1). *Micrometastases* are classified as M1. The report should specify that it is a micrometastasis: M1 (mic) [25]. *Isolated tumour cells* should be classified as M0.

Early Invasive Rectal Carcinoma: Risk Factors for an Adverse Outcome

Rectal adenomas containing invasive adenocarcinoma extending though the muscularis mucosae into the submucosa have been defined as "malignant polyps". These polyps constitute a form of early (i.e., curable) rectal carcinoma. Various opinions exist for managing patients after endoscopic removal of malignant polyps. One possibility is that all patients with malignant polyps should undergo standard resection [65]; another opinion is that a conservative approach should be maintained under the condition of an absence of cancer at the resection line [66]. Malignant polyps removed by endoscopic polypectomy require evaluation of histologic parameters that have been determined to be significant prognostic factors related to the risk of adverse outcome (i.e., lymph node metastasis or local recurrence from residual malignancy) after polypectomy [4, 26, 38, 66–80]. Pathologic features having independent prognostic significance and that are crucial for evaluating risk of adverse outcome and determining the possible need for surgical treatment include histologic grade, level of invasion of the submucosa, status of resection margin, and lymphatic–venous vessel involvement. A matter of controversy involves which parameters should be integrated into such criteria relating to tumour aggressiveness such as tumour "budding" and extension (width and depth) of invasion in the submucosal layer.

By using 3 qualitative parameters for cancer (tumour grade, vascular invasion and budding) we might be able to select patients having a lower possibility of nodal involvement. The absence of an unfavourable tumour grade, definite vascular invasion and tumour budding would be the most informative combination of criteria for selecting patients with low recurrence risk and are ideal for conservative approaches. The nodal involvement rate is 0.7%, 20.7% and 36.4% if one, two or all three parameters are unfavourable [81].

Numeric data regarding extent of submucosal invasion aid in choosing tumours having very little risk for nodal involvement (width of submucosal invasion <4000 μm; depth of submucosal invasion <200 μm) in patients with an absence of unfavourable parameters [81].

Ueno [82, 83] has also reported that the qualitative parameters observed in the biopsy specimens of the submucosal horizontal invasive frontal region in advanced rectal cancers are relevant to the extent of extramural and intramural spread. It can be assumed that these parameters are appropriate to evaluate the potential for invasion and metastasis.

Tumour Regression Assessment After Pre-Operative Therapy

Tumours treated prior to surgery may show marked macroscopic and histologic alterations compared to conventional colorectal tumours. The macroscopic characteristics of the lesions are quite different from the "original" ones; sometimes lesions disappear and in most cases they leave a white area that resembles a scar. When there is no macroscopic evidence of the lesion or when there is a scar-like lesion, the entire area should be submitted for histologic evaluation. Cases following radiotherapy may have very few lymph nodes. In these cases, the pN can still be assessed and nonetheless appears to have a prognostic significance despite the small number of lymph nodes.

From a histologic standpoint, it is important to evaluate the presence of residual disease in addition to the effects of therapy and the entity of the residual tumour [84, 85] (Table 5). The report should state all prognostic parameters used for conventional carcinoma including the distance of residual lesion from the circumferential (radial) margin. Pathologic stage remains one of the most important prognostic factors following neoadjuvant therapy. Patients with disease downstaging have significantly better survival [86–88].

Table 5. Tumour regression grade (TRG) assessment

TRGrade 1: absence of residual tumour (complete regression)
TRGrade 2: rare residual tumour cells scattered throughout the fibrosis
TRGrade 3: increase in the number of residual tumour cells but fibrosis still predominates
TRGrade 4: residual tumour cells outgrowing the fibrosis
TRGrade 5: absence of any tumour regression

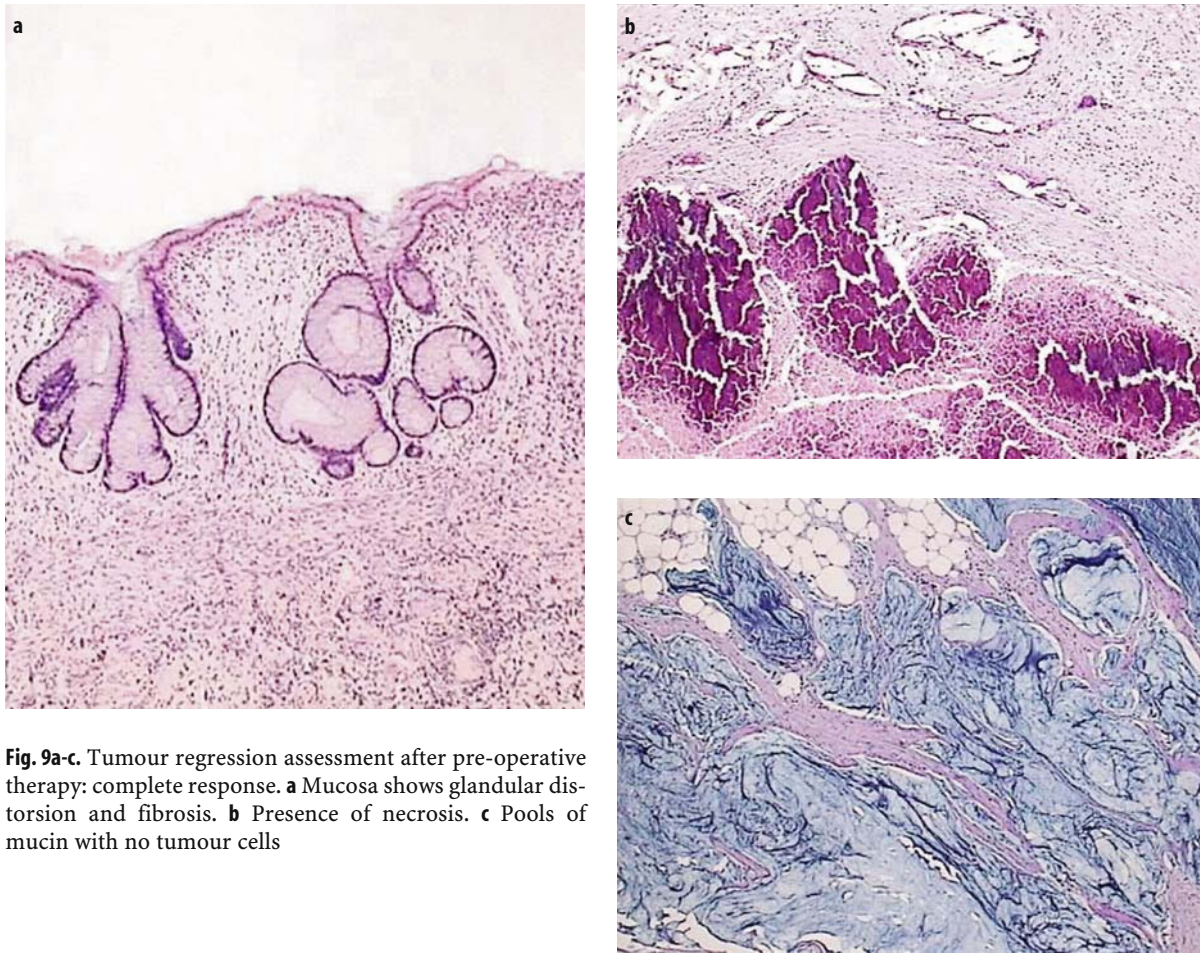


Fig. 9a-c. Tumour regression assessment after pre-operative therapy: complete response. **a** Mucosa shows glandular distorsion and fibrosis. **b** Presence of necrosis. **c** Pools of mucin with no tumour cells

Microscopic examination can reveal a complete response to therapy with no residual disease. These cases generally show marked submucosal fibrosis sometimes involving the muscularis propria with thickening and doubling of muscularis mucosae; areas of necrosis may be seen with no residual tumour. In some cases the tumour can disappear, leaving the adenomatous component at the edge of an ulcer (this "resistance" might be explained by a lower cellular turnover). Even if there is an adenomatous component, response to therapy can be considered complete. On occasion, pools of mucin with no tumour cells located within the rectal wall or in the lymph nodes can be observed (Fig. 9). The significance of this finding is not yet understood, even though it should be stated in the pathology report. Residual carcinoma can range from a few poorly differentiated, pleomorphic tumour cells (partial response) to extensive areas of tumour infiltration through the wall or the perirectal tissues, very similar to non-treated lesions (poor or absent response) (Fig. 10).

A 1 to 5 grading system has been proposed [84] to evaluate tumour regression. This system is based on residual disease and fibrosis, as proposed by Mandard et al. for tumours of the oesophagus treated by neoadjuvant radio- and chemotherapy [89]. Disease downstaging is related to a much better prognosis for disease-free patients; the presence of a stromal response in terms of fibrosis with scant inflammatory infiltrate and the absence of ulceration are related to a reduced disease-free survival [90].

Future Perspectives

The search for new pathologic markers, different from the presently used morphologic ones, will increase the understanding of tumour biology, predictive rates and will improve therapies for each individual patient. In the absence of clear prognostic factors, oncologists may choose subjectively whether to perform surgery alone or to utilise adjuvant therapies. At present, tumour stage is still the most signif-

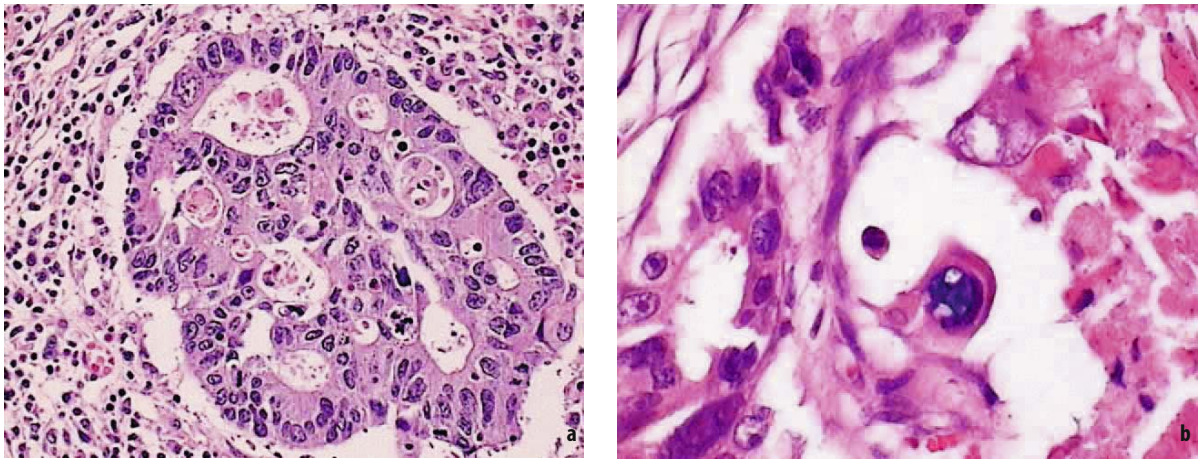


Fig. 10a, b. Tumour regression assessment after pre-operative therapy: residual carcinoma. **a** Residual neoplastic gland. **b** Poorly differentiated pleomorphic tumour cells

icant prognostic factor, but as tumours at the same stage may have different outcomes, new markers are needed to further subdivide tumours in term of prognostic and response to therapy.

Some of the genetic alterations identified in colorectal carcinomas may be used as prognostic markers [91, 92]. Loss of chromosome 18q in stage II tumours (Dukes B) has been shown to be a good marker that predicts a high risk of metastasis and can be used to select tumours that will benefit from adjuvant chemotherapy [9]. High levels of microsatellite instability have been shown to be a positive prognostic marker, independent of stage [93, 94].

The absence of p27 expression seems to correlate with poor prognosis. None of the current markers can predict response to therapy, although selected molecular alterations may gain significance in the foreseeable future. Studies on colorectal tumour cell lines have shown that p53 status seems to have a role in the response to chemotherapy [95]. It has also been shown that MSI tumours are resistant to cisplatinum [96, 97] but sensitive to radiotherapy [98] and 5-FU [99]. Radio-sensitivity is related to p53, p21 mediated apoptosis; tumours without p53 mutations are more sensitive to radiotherapy [100]. Tumour stage and pTNM for resected patients are the most important prognostic factors that influence therapeutic strategies. While molecular markers are still not part of the staging system, they should be included in the pathology report whenever available.

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TME: How to Interpret the Favourable Results?

Leif Hultèn, Gian Gaetano Delaini, Marco Scaglia, Gianluca Colucci

Introduction

As for surgical tumour management in general, the principal for radical rectal cancer surgery is removal of the primary tumour, including the regional lymphatics and prevention of tumour cell spillage (Table 1). Even after several decades of evaluation and research, controversy still exists as regards the extent of lymphadenectomy, the importance of the no-touch principle, the optimal free distal margin and the irrigation/washout of the rectal stump.

Although there may be surgeons today who apply Turnbull's "no-touch technique" [1], it is doubtful if it is of any major benefit [2]. Moreover, while for some surgeons 'wide lymphatic excision' means a "high tie" of the inferior mesenteric artery with inclusion of mesenteric lymphadenectomy, to others it means complete retroperitoneal clearance of all lymphatic tissue – i.e., pre-aortic as well as precaval lymph nodes ("pre-aortic strip"). Such a procedure enables removal of additional lymphatic tissue, but whether this confers an advantage in survival is unproven. Extended lateral internal iliac lymph node excision has been on trial in many series but there are no randomised clinical trials supporting its value. Proximal nodal involvement at the level of the inferior mesenteric artery, these nodes may indicate a high likelihood of systemic spread and then a low possibility of cure, regardless of the extent of surgery. Moreover, the price paid for such an extended surgery is a high incidence of urinary and sexual complications owing to autonomic nerve damage.

For the radical excision of a rectal cancer, a generous distal free margin below the tumor has been an important issue. The well known "5-cm rule" was based on careful pathological investigations of the intramural tumour spread [3]. The measure was put into practice during the 1960s and was applied for a long time by most colorectal surgeons. However subsequent studies have shown evidence that intramural spread only occasionally exceeds 1–2 cm and that further increase of the distal margin beyond 2 cm does not improve the locoregional recurrence rate or survival [4]. It has been an established principle that the mesorectum and the wall of the rectum should be transected at the same level.

Table 1. Controversial issues in rectal cancer surgery

"No-touch" technique?
Proximal clearance – "High tie/'pre-aortic' strip"?
Distal clearance – "a 2- or 5-cm rule"?
Lateral clearance – extensive lymph node dissection?
Total mesorectal excision (TME)?
Circumferential radial margin (CRM)?

In contrast to many of these unconvincing attempts and doubtful results mentioned to improve radicality in rectal cancer surgery, the introduction of "the new surgical technique" – total mesorectal excision (TME) – presented by Heald et al. [5], has proved to be extremely effective, particularly by reducing intrapelvic recurrences. The technique has made a considerable impact on rectal cancer treatment worldwide. Heald's concept of the operation was based on the evidence of isolated metastases within the mesorectum distal to the primary tumour (Fig. 1) [6, 7]. The removal of the distal mesorectal tongue was considered to be the main secret of success. Although the incidence and location of the retrograde tumour extension into the mesorectum was seriously questioned, TME rapidly became the "gold standard" technique worldwide for anterior resection of the rectum and a marked reduction of local recurrence rates has been presented from many colorectal centres having adopted this technique (Table 2) [8-10].

Heald's TME procedure involved a meticulous sharp dissection of the entire mesorectum with the aim of removing tumour that had locally spread even via other mesorectal lymphatics. The plane of dissection extends along the avascular areolar plane outside the perirectal fascia – "the holy plane". As the sharp dissection is continued downwards, the anorectal ring is reached eventually, at which point the lowest part of the mesorectum is dissected free with removal of the distal "mesorectal tongue". The use of

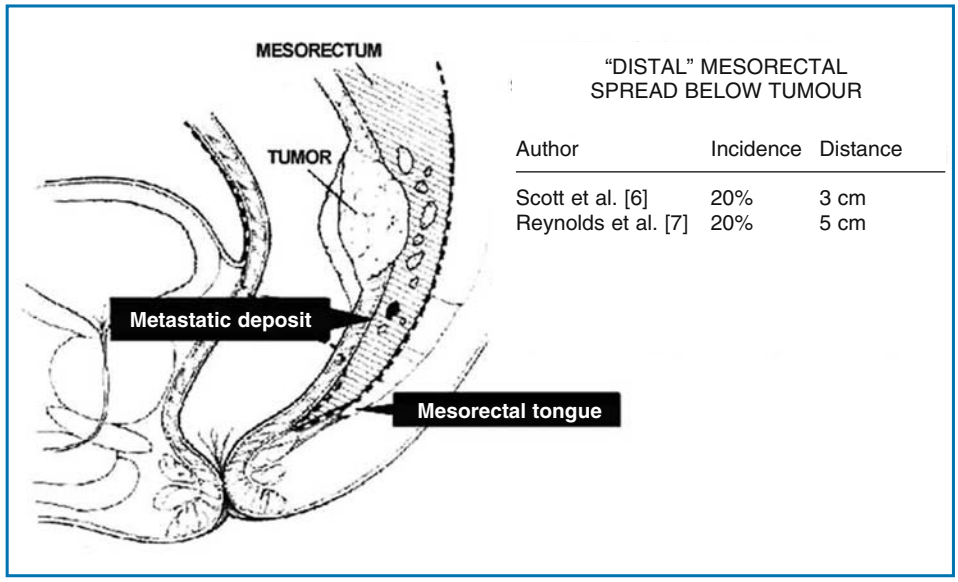

Fig. 1. Total mesorectal excision (TME) according to Heald, 1982 [5]

Table 2. The locoregional recurrence rate at 4 years

Authors	Conventional technique (%)	TME technique (%)
Arbman et al. [8]	23	8
Havenga et al. [9]	32	9
Wibe et al. [11]	12	6

sharp dissection to develop the "holy plane" rather than blunt finger dissection was emphasised by Heald as a particularly important measure thought to lessen the risk of rupturing or tearing the mesorectal fascia, thus spreading tumour cells. Apart from total excision of the mesorectum, the procedure includes a radical proximal lymphatic excision performed by ligation of the inferior mesenteric artery 1 cm off the aorta and ligation of the inferior mesenteric vein 1 cm from the splenic vein but without an extra mesenteric 'pre-aortic strip'.

Heald's paper on the technique was criticised and the favourable results questioned, and the introduction of the TME principle started an intense debate with revival of interest in the details in pelvic anatomy and its curative value and indications for its use [10, 12-14].

In the original paper Heald stated that the main problem leading to high local recurrence rates in many studies was that isolated metastases within the mesorectum distal to the primary tumour were left behind. The article was interpreted as recommending removal of the entire mesorectum in all rectal cancer cases, regardless of the level of the rectal cancer. This statement has been seriously questioned however. The removal of the distal mesorectal tongue could not possibly be the sole explanation for the improved results, because recurrences develop frequently even after total abdominoperineal rectal excision in which all mesorectum is removed and the results in many other studies on rectal excision for cancer had demonstrated comparable local pelvic recurrence rates without taking out the entire mesorectum. Moreover, although mesorectal deposits can occur well distal to the tumour, the prevalence is considered too low to justify excision of the whole mesorectum to the level of the levator ani. The consequences would be a great number of ultralow anterior resections being done unnecessarily for tumours even in the upper third of the rectum, putting the patient at increased risk of anastomotic leakage and poor function [15]. Subsequently, the removal of the distal mesenteric tongue has been considered excessive as a standard procedure being indicated preferentially for low sited tumours. Therefore – in its present properly defined form – TME is recommended for distal mid- and lower rectal cancer, with complete excision of the visceral mesorectal tissue down to the level of the levators (Fig. 2, left panel), whereas for upper third or rectosigmoidal cancer a *tumour-specific mesorectal excision* (TSME) should be preferred, which means a precisely perpendicular and circumferential excision of the mesorectum to the level of an appropriate resection margin distal to the tumour (mostly 5 cm recommended) (Fig. 2, right panel).

The anatomical basis for the TME principle is certainly not new. It was very carefully defined by Jonnesco [16] and Bissett et al. [13], putting emphasis on

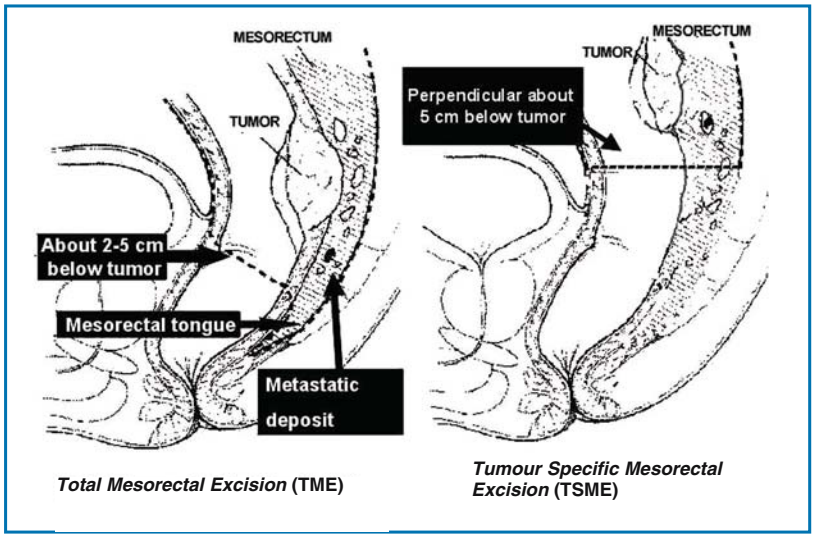

Fig. 2. TME reserved for low tumours and TSME for more prox. tumours

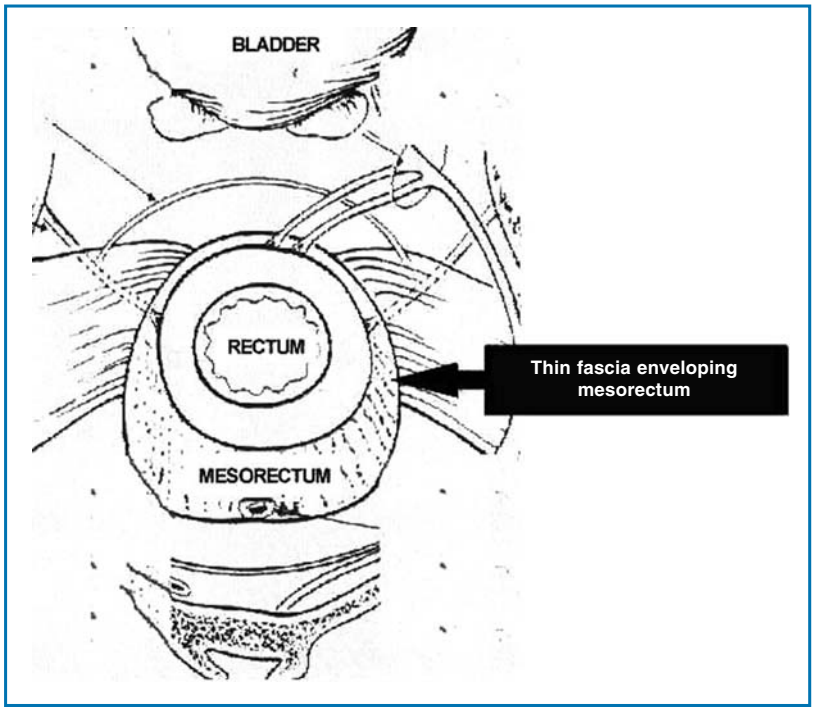

Fig. 3. The importance of keeping the circumferential radial margin (CRM) clear. Local recurrence may result from an incomplete radial resection rather than from an incomplete distal mesorectal excision

the fact that mesorectum is enveloped in a thin fascia, and that violating the fascia may compromise radicality, increasing the rate of local recurrence [17-19]. The description of the fascia propria plane also emphasises the importance of an adequate circumferential margin (Fig. 3) and it may well be that the main value of the TME procedure may be attributed to the ability to keep this margin clear. Local recurrence may result from an incomplete radial resection, although the surgeon may not always be capable of knowing whether this margin is clear of disease. It has been demonstrated that about 25% of cases may have unsuspected involvement of the radial margin after rectal excision. And leaving residual disease at the cut radial margin would mean that recurrence is inevitable. TME has been shown to decrease the rate of positive radial margins and this may be one of its main impacts on prevention of local recurrence [20-22].

Local recurrence may result from an incomplete radial resection rather than from an incomplete distal mesorectal excision. Heald changed the emphasis

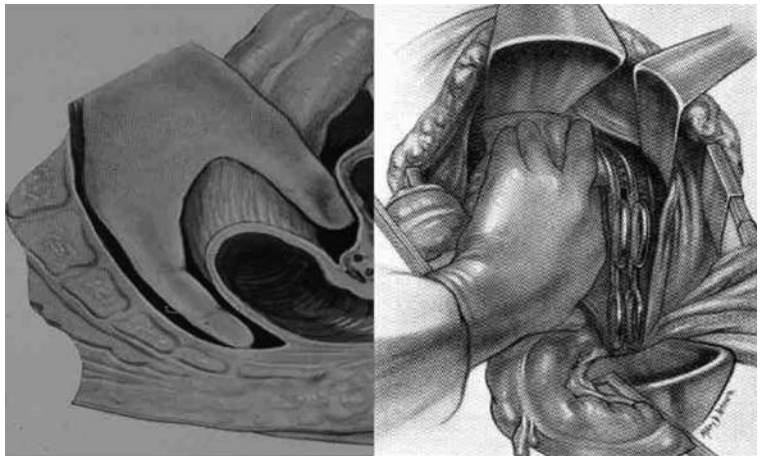

Fig. 4. The rude, blind and blunt dissection technique as it is often illustrated in traditional textbooks

subsequently from the extent of distal dissection or radial dissection to minimising the transection of perirectal lymphatics by keeping the fascial envelope intact.

The recent literature has in many respects been very confusing and unfortunate on this issue. Heald may not have discovered a superior unrecognised technique and his results may well be questioned, but it is beyond dispute that his contribution has been extremely important. He has defined more clearly than most others exactly what he is doing and in a way that others can readily duplicate. It is reasonable to assume that the dramatic reduction in local recurrence that has been recently reported from many surgical units may simply reflect the poor effectiveness of surgical technique employed prior to the introduction and training of the TME technique. Although scientifically unproven, there is strong evidence to show that the sharp dissection under full visualisation – preferably aided by means of a head lamp – is superior to a blunt and partly blind dissection technique, and should be very important to avoid ploughing into the wrong dissection plane. Judging by the illustrations shown, even in well known recently published textbooks, the blunt dissection technique seems to be quite common even in expert hands (Fig. 4).

The TME technique has to be rigorously tested in a prospective, randomised trial to throw light on these issues.

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Lateral Pelvic Lymph Node Dissection (LPLD) in Rectal Cancer: an Overview

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Introduction

Rectum carcinoma grows relatively slowly and behaves more favourably than other gastroenteric neoplasias [1]. These biologic features are also often observed in lymph nodal and hepatic metastases [2]. Among the ways of spreading, haematogenous is the most belated, whereas lymphatic is the most precocious [3]. Most patients (65–80%) have shown that their illness has primarily spread around the rectal wall (T3N0M0), and/or involving the mesorectal lymph nodes (N1–2M0), which is a manifestation that represents a stage of locoregional illness [4]. Therefore, for most of its natural history, surgical therapy has an important role in the treatment of rectal cancer [1, 5].

The oncological premises of rectum resective surgery have been known for almost a century, that is since Miles [6] and Moyniham [7] recognised the importance of the anatomy of the lymphatic drainage system as a guide to the extension of a proper exeresis of the cancer.

However, the application of these principles in clinical practice has varied greatly. The "optimal" surgical treatment of rectal cancer is yet to be studied in its entirety, and there is no unanimous agreement about the extension to be given to lymphadenectomy [8, 9]. While for some surgeons an extended lymphatic exeresis means performing a high ligation of the inferior mesenteric artery associating it with the mesenteric lymphadenectomy, for others it is configured with the complete removal of the retroperitoneal lymphatic tissue [5].

Western surgeons consider the mesorectum as the main way rectum carcinoma spreads [10, 11, 12], and its complete removal (total mesorectal excision (TME)) as necessary and sufficient for radical surgical treatment of rectal cancer [1, 4, 13].

Japanese surgeons are very careful to prevent the extramesorectal spread to lateral pelvic lymph nodes [2, 14], which may be found in 10–25% of rectal neoplasia localised underneath the peritoneal reflection [2, 3, 12]. Because such lateral spread verifies and exceeds the limits identified by Quirke within the margin of circumferential resection [15], it would be necessary, according to Japanese surgeons, to perform the extension of lymphadenectomy to the nodal pelvic iliac-obturator stations (lateral pelvic lymph node dissection (LPLD)) [2, 3, 14].

This "ultra-radical" surgery, although it is convenient in terms of local relapses and long-term survival compared with more limited lymphectomies [3, 14], is burdened with a high percentage of genito-urinary disturbances [16]. These functional consequences, together with evidence of local and long-term tumour control after performing TME without using LPLD, which are just favourable as those obtained with LPLD [4, 11], did not favour the acceptance of LPLD in Europe and in the United States; also considering the "Western" point of view which interprets the metastasisation of lateral pelvic lymph nodes as no longer a regional but a systemic illness, which must then be treated using (neo)adjuvant radiochemotherapy strategies [4, 10].

Rectum Lymphatic Drainage and Patterns of Lateral Lymphatic Involvement in Rectal Cancer

Rectum lymphatic draining system is rather complex and is performed in 3 directions:

1. *ascending* down the higher haemorrhoidal–inferior mesenteric arterial peduncle to the para-aortal lymph nodes;
2. *lateral* down the middle haemorrhoidal artery to the iliac and obturator lymph nodes;
3. *descending* down the lower haemorrhoidal artery to the inguinal lymph nodes.

The direction of the lymphatic flow depends on the rectal site, the ascending way representing a lymphatic discharge common to the whole rectum, and the lateral way constituting an almost exclusive draining of the lower rectum and of the anal canal above the pectinate line [2, 17]. According to Heald and Moran [18] and Stelzner [10], the main metastatic spreadway starts from the mesorectum with an ascending polar-

ity, whereas a caudal and lateral dissemination would represent a rather rare event (1–2%), always secondary to the retrograde lymphatic spread in the case of very advanced neoplasias [8, 10]. Some lymphoscintigraphic studies highlight the lymphatic flow as almost exclusively down the higher haemorrhoidal lymphatics–inferior mesenterics, and do not show any connection between the internal iliac lymph nodes and the inferior mesenterics [19, 20].

Arnaud et al. [21] remark, however, on a pattern of lateral lymphatic draining to the internal iliac lymph nodes in 50% of control cases using the same method.

In the 1920s Villemin et al. [22] in France and Senba [23] in Japan, in anatomy and post mortem studies showed the existence of lateral lymphatics, starting from the lower rectum (beneath the Houston middle valve), spreading around the internal iliac arteries and inside the obturator regions as well.

In 1951, Sauer and Bacon [24], while performing a pre-operative injection consisting of a colouring substance in the lower rectum mucosa, confirmed the presence of a lymphatic flow down the middle rectal vessels, inside the lateral ligaments, emphasising the opportunity to perform a lymphadenectomy extended to the lateral ligaments and to the iliac vessels to control the lymphatic spread of lower rectal cancer [9, 24].

If the historical evaluations pointed out a neoplastic lateral spread in the 0–9% range [8], more recent and detailed pathologic studies show that such an event occurs in 23–41.8% of patients having rectal cancer below the peritoneal reflection [3, 17, 25].

Lateral metastasis is usually associated with the presence of pararectal positive lymph nodes, and it represents an isolated event in about 5% of cases [25]. Pelvic nodes that are more frequently involved are the ones down the middle rectal artery (11%), the obturator pelvic nodes (8.9%) and internal iliac pelvic nodes (6.4%) [25].

The remark that rectal cancer has a relatively slow locoregional progression and anatomy and clinical data suggesting the existence of a primary and precocious relay to lateral lymph nodes (at least regarding the low rectum) [26], give a theoretical explanation for the adoption of more extended lymphadenectomies [2, 14, 17, 24].

Lateral Pelvic Lymph Node Dissection (LPLD). Technical Notes, Indications, Results and Complications

LPLD consists of a complete dissection of the endopelvic fascia together with the rectum and mesorectum [9]; the first phase is represented by the complete removal of the para-aortic and paracaval tissues, from the left renal vein, up to the aorto-caval bifurcation. Starting then from the aorto-caval bifurcation, and using ureters as lateral dissection limits, all lymph nodes as well as the lymphatic–cellular tissue are removed medially to the common and internal iliac vessels [5, 9]. Moreover, the clearance of the obturator region is performed preserving the nerve [9]. In case of metastatic, or suspected lymph nodes located down the iliac vessels and in the obturator foramen, some surgeons remove the hypogastric vessels completely, preserving the superior vesical artery and the obturator nerve [2].

The likelihood of rectal cancer hitting the lymphatic system depends on its stage and it may reach 70% in the case of complete parietal penetration or of infiltration of nearby organs. It is these patients having parietal extension (u)T3 and (u)T4, and stage III TNM who are mostly likely to undergo an LPLD [2, 9].

Pre-operative selection is based on combined information given by pelvic TAC and RNM, and by rectal endosonography. In a perspective evaluation of lateral pelvic lymphadenopathy there is a critical diagnostic limit for lymph nodes of <5 mm [2], and moreover it must be taken into account that the lymph nodal intraoperative staging performed by the surgeon is not very accurate [25].

Sauer and Bacon [24], Stearns and Deddish [27] and St. Mark's Hospital's surgeons [28] were the first to apply LPLD but without any remarkable results in terms of local relapses and survival. Enker et al. [29] renewed interest in LPLD, managing to improve the survival of patients having Dukes C stage in comparison with those who underwent ordinary surgery.

One of the best documented experiences was proven at the National Cancer Center Hospital in Tokyo [3, 16], where LPLD results were considerably higher than results obtained performing ordinary lymphadenectomy surgery both regarding long-term survival (88% 5-year Dukes B and 61% Dukes C *vs.* 74% and 43%) and regarding local relapse control (6.3% Dukes B and 23.6% Dukes C *vs.* 21.8% and 32.9%).

Moriya et al. [2] consider LPLD to be particularly effective in the treatment of Dukes C stage (55% 5-year survival free of illness, 16% pelvic relapses) and presented a remarkable 5-year survival of 43% in patients presenting with lateral lymph nodal metastasis, especially if compared with curability percentages lower than 10% in former experiences [3].

Suzuki et al. [13] emphasise that the extension of lymphadenectomy is a decisive factor in preventing local relapses.

Surgical mortality in LPLD is low, ranging from 0.7 to 2.1% [2, 16, 29], but there is an increase of intraoperative blood loss [16, 29], of complications, and a serious problem with genito-urinary function-

ality [16, 25]. Eighty per cent of patients complain of post-surgery bladder disorders, 40% complain of lack of a bladder kick sensation and 76% complain of impotency; these percentages are twice as high as those of patients who underwent ordinary surgery [16]. This is the consequence of sacrificing pelvic autonomic nerve structures [30].

With the aim of reconciling radical needs with an appropriate lifestyle, Japanese surgeons developed extended lymphadenectomies by preserving pelvic nerve structures (LPLD-nerve sparing – NS) [30, 31]. The extent of the preservation of nerve structures may be total or partial (complete or partial sparing of the contralateral hypogastric nerve, or of the pelvic plexus, performed on one side or on both) [30, 31] and depends on where the tumour is located, its grading and stage [32].

Although some histopathologic reports discuss the opportunity to perform nerve-sparing operations because of the possibility of a perineural invasion of the pelvic plexuses [33, 34], clinical experiences are rather favourable. Five-year survival is 74–91.7% in Dukes B patients, and 56.7–67.3% in Dukes C patients [31, 35]; local relapses are about 4.8–7.9% [30, 31, 35].

As for functional results, after a (partial or total) LPLD-NS, appropriate urinary function is maintained by 78.6–93.2% of patients, effective potency is maintained by 31.2–71.3% of patients and an ability to ejaculate is maintained by 6.5–53% of the cases [30].

Comparison Between TME and LPLD in Surgical Treatment of Rectal Cancer

Although some studies on LPLD show a tendency of oncologic results to improve [2, 16, 31], the technique did not earn wide consent because of the lack of incontrovertible data about its effectiveness [1, 4, 5, 9, 12].

Recently, Moreira et al. [36], comparing the patients who were operated on with or without LPLD, observed that relapses, metastasis and survival are connected with adverse pathologic factors (such as venous and perineural invasion), and not with the extension of lymphadenectomy.

Among the various arguments against the routine use of LPLD are the relatively low number of cases presenting involvement of lateral lymph nodes (6–15% of the total number of patients having rectal cancer) [3, 12, 30], consistent increase of surgical time and complications [4, 8], severe damage to the genito-urinary function [12, 30], and the negative prognostic outcome of lateral lymphatic metastases (5-year survival 7.1–26%) [3, 12, 30].

The most consistent criticism of the Japanese results is the lack of a clinical perspective and randomised evaluation that can definitively clarify the various debates that have arisen [4, 5, 9, 25, 37].

From a practical point of view the adoption of TME in various European centres as well as in the United States contributed to decreases in local relapses to considerably below 10% [4, 37, 38]. Both McFarlane [11] and Enker [4] report local relapses of 5–8% and a 5-year survival free of illness in 74–78% of "high risk" patients (T3N0M0, T3N1–2M0), results which equal those obtained with LPLD [4, 9]; however it must be pointed out that Western series report cases of tumours above the peritoneal reflection [1, 39, 40], where lateral lymph nodal metastases are very rare [17, 35].

Further benefits of TME are represented by a considerable decrease of abdominoperineal amputations [1, 38], preservation of bladder function in almost all patients and preservation of sexual function in over 80% of cases (autonomic nerve preserving TME) [38, 39]. In Heald's [1] and Enker's [4] opinion, TME and LPLD, even though different, obtain similar results because they are based on a thorough dissection down well defined anatomic–embryologycal planes, and both ensure undamaged circumferential resection margins in over 90% of cases [37], which is a prerequisite for the local control of rectal cancer [15].

We must not overlook the recent Japanese experiences showing survivals much higher than 50% at 5 years after LPLD in patients with lateral lymph nodal metastases [17, 41, 42].

Takahashi's remarks [17] about the bad results reported by Heald and Enker in patients with cancer within a 5 cm limit from the anal margin who underwent abdominoperineal amputations (33% local relapses and 42% long-term survival), and the data of the CKVO 95-04 Dutch trial of 20% local relapses after TME in stage III patients [43], would seem to be indirect proof that a considerable amount of neoplasias in the low rectum spread beyond the reach of the TME alone [17, 44].

When neoplastic involvement is lower than 4 lymph nodes [42], or if it is exclusive of the lateral lymph nodes [17], 5-year survival is 75%, compared with 65% of cases with metastasis of mesorectal lymph nodes (17%). It is then possible that some specific subgroup of patients may benefit from LPLD [41, 42]. The problem, which is still unsolved, is how to select the patients pre-operatively [4, 42].

It has been widely confirmed, in the Western side of the world, that pre-operative radiotherapy considerably reduces local relapses both associated with ordinary surgery and with TME (especially in N+ patients) [44, 45].

The effectiveness of pre-operative RT associated with nerve-sparing surgery in the case of advanced

rectal cancer in terms of local control and preservation of urinary function was also recently confirmed by Japanese surgeons [46]. Moreover Watanabe et al. [47] compared the patients who underwent LPLD or ordinary lymphadenectomy preceded by RT (50 Gy), without finding any difference in terms of global and illness-free survival and local relapses, suggesting that pre-operative RT may be a good alternative to LPLD because of the cytotoxic effect on regional lymph nodes, including lateral lymph nodes as well.

Conclusions

Recent anatomic–surgical research [17, 26], together with clinical experience [17, 41, 42], has reaffirmed the importance of the lateral lymphatic spread in cases of neoplasia of the lower rectum (within 5 cm of the pectinate line) [17], which may still be considered in some cases as a surgically curable illness [17, 41, 42].

It is still not definitely clear whether involvement of lateral lymph nodes is an indicator of a severe prognosis, or of the opportunity to perform an LPLD [48], nor has the most suitable therapeutic strategy been clarified [32, 42, 49].

Selected subgroups of patients (exclusive metastases of lateral lymph nodes, involvement of only one group of lymph nodes of the lateral compartment, fewer than 4 lymph nodes involved) may avail themselves of an LPLD [41, 42], considering that also TME offers suboptimal results in very low and advanced rectum localisations [17, 44].

The difficulty which has not yet been overcome is the pre-operative selection of these patients, representing 6–15% of all cases of lower rectal cancer [4, 42].

Recent remarks [48] suggest reinvestigating the role of extended but selective lymphadenectomy employing the technique of lymphatic intraoperative mapping with sentinel node [25, 26].

Pre-operative radiotherapy, in concurrence with an exeresis following TME's principles, was shown to be equally as effective as LPLD [47].

In 2001 in Japan a "TME *vs.* LPLD-NSS" randomised clinical trial for stage II or III lower rectal cancer was started, to clarify how to treat lateral lymph nodal metastases and which patients ought to be treated with LPLD [32].

Moriya [49] emphasises though that so far in Japan adjuvant treatments have been considered less often, and that there is a need for controlled studies testing TME+RT *vs.* LPLD-NSS.

At the moment diagnostic imaging tests do not allow prediction of the behaviour of a malignant tumour of the rectum as regards its lymphatic spread. In the near future a more accurate pre-intraoperative staging as well as molecular biology methods will be able to confirm, on the basis of a more thorough assessment of lymphatic spread, which patients need a local exeresis or a wide resection, performed alone or in combination with (neo)adjuvant therapies [25].

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Controversial Issues in Rectal Cancer Surgery

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Introduction

Ernest Miles [1] postulated that adequate treatment of rectal cancer, regardless of the site and apparent progress of the tumour, in all cases necessitated a wide excision of the entire anorectum and establishment of a permanent colostomy by an operation involving both an abdominal and a perineal dissection. Lloyd-Davies confirmed this statement, advocating the synchronous combined technique that became by far the most popular method of dealing with rectal cancer worldwide.

However, from the early 1940s onward, sphincter-saving methods, even low anterior resections, were put on trial by several surgeons [2]. The results for growths of the rectosigmoid and upper third or half of the rectum proved to be good and with the passage of time surgeons were encouraged to extend the use of these methods to yet lower lesions. One disadvantage was that low-sited tumours were often inaccessible for technical reasons, and many different techniques were used to overcome this problem [3, 4]. Moreover, a handsewn anastomosis was often associated with a high incidence of leaks, fistulae, abscesses and anastomotic strictures, and the functional results were often unsatisfactory. Although patient satisfaction was stated to be positive in the majority of patients, flatus and/or faecal incontinence were common. Based on a careful assessment of the functional results after low anterior resection, Goligher et al. [5] concluded that if a rectal stump of at least 6–7 cm could not be preserved, the patient would be better treated by abdominoperineal resection (APR).

With the advent of stapling instruments allowing mechanical construction of the colorectal anastomosis and the contribution of the colon pouch, ultralow anastomoses have become routine procedures performed by most general surgeons. Anterior resections (ARs) with anastomosis are now possible at a level that could never be performed by handsuturing. The lowest rate of permanent stoma formation for rectal cancer in the literature is below 10%, in a unit routinely employing a stapled anastomotic technique for low anterior resection [6], and other specialist units have reported similar low rates [7], figures that differ greatly from the more common rates of about 30% [8].

Radicality

Numerous trials have been done over the years to evaluate the oncological merits of the two operations and no difference in the pelvic recurrence rate or disease-free survival has been demonstrated. There are no randomised studies to confirm this and such a study will probably not ever be done. So, the general opinion held is that a correctly performed AR for a rectal cancer should not decrease the curative potential when compared to an APR, and should give as good a long-term cure as the APR.

The appearance of a local pelvic recurrence both after an AR or an APR has been a disappointing event over the years but the recent introduction of total mesorectal excision (TME) – a proper anatomical dissection technique advocated by Heald et al. [9], has been a great step forward by reducing the recurrence rate considerably. Special attention is directed towards the importance of a TME – which rests on the recognition of the distal mesorectum as a possible site of tumour spread – and on the recognition of an inadequate circumferential margin outside the mesorectal fascia [10]. Subsequently the removal of the distal mesenteric tongue has been considered excessive as a standard procedure. Therefore – in its present form properly defined – the TME with complete excision of the visceral mesorectal tissue down to the level of the levators is recommended mainly for distal mid- and lower rectal cancer (at or below 12–13 cm above the pectinate line); whereas for the upper third or rectosigmoidal cancer a tumour-specific mesorectal excision (TSME) should be preferred, which means a precisely perpendicular and circumferential excision of the mesorectum to the level of an appropriate resection margin distal to the tumour. The current most popular view is that the

distal intramural spread below the tumour is a rare event and a free distal margin of 2 cm below the tumour is considered adequate [11].

Morbidity and Mortality

A sphincter-preserving operation that aims to improve quality of life (QoL) must also be safe to perform with a low mortality and morbidity and must give a satisfactory functional result.

It is well known that APR is associated with a significant complication rate both related to the perineal wound and the abdominal stoma. In a recent study [12] the overall complication rate was reported to be about 60%, the most frequent being urinary tract problems and perineal wound infections. However, even AR proved to be afflicted with an overall complication rate approaching 40%; anastomotic leakage and pelvic sepsis (10%) being the most frequent. However the adoption of the TME technique leads to an increasing number of low and ultralow colorectal anastomoses and with them an increased complication rate, as reflected in a report from Karanjia et al. [6]. The leakage rate in this study was 18%, mostly in patients with an anastomosis fashioned below 6 cm.

Major leaks occurred in 24 of the 219 patients in the study. Three of these patients died and the remaining 21 patients ended up with a permanent stoma. Mortality rates after the two operations seem to be similar, ranging between 2 and 3% [13].

It should be emphasised however that APR and AR are technically and anatomically quite different procedures and therefore not comparable. Problems related to the perineal wound after APR add considerably to the morbidity.

Comparative Aspects

The APR has often been referred to as a formidable operation associated with significant changes in body image. Devlin et al. [14] and Williams and Johnston [15] painted a very gloomy picture of colostomy patients' QoL, the majority suffering from leakage and odour restricting their social life. However, although an AR leaves patients' body image intact, the procedure may be associated with considerable functional disturbances. Excision of tumours in the mid and distal third of rectum means sacrifice of the major or entire part of the rectal ampulla thereby interfering with the delicate recto-anal nervous control of defecation and continence. Increased evacuation frequency, defecation urgency and imperfection of continence is inevitable, occurring in between half and two thirds of patients, with increasing severity the lower the colo-anal anastomosis [16, 17]. The use of pre-operative radiation contributes to further deterioration of function [18].

From these results, it seems that a rectal stump of about 6 cm from the anal verge is necessary to maintain reasonable recto-anal function, confirming the statement of Goligher et al. [5]. As a shorter stump may confer worse function, the fashioning of a short 5–7-cm colon J-pouch or alternatively a coloplasty procedure created by making an 8–10-cm longitudinal colostomy above the anastomosis and closed transversely with two layers of sutures has been advocated in an attempt to restore a neo-rectal reservoir and such trials have proved to be beneficial [19, 20]. It should be mentioned however that, apart from being demanding procedures with specific inherent complications, functional imperfections still remain (evacuation difficulties and incontinence) and long-term effects are unknown. The traditional view of low anterior resection seems now to have been modified to comprise total rectal excision with colopouch anal reconstruction as the standard restorative operation for tumours of the mid and lower rectum.

Quality of Life Assessment

Sphincter-saving procedures are today considered to be the first choice in the treatment of even very low sited rectal cancer. One may get the impression that an AR should be done whenever possible and at any cost, restricting the use of APR to a small proportion of cases where the lesion actually invades or approaches very closely to the anal canal. The main reason for this has been the conviction that the QoL for patients with a colostomy after APR was poorer than for patients undergoing a sphincter-preserving technique. However, such statements often date from older reports at a time when sanitary and stomatherapeutic standards were poor [15]. Stoma care has improved considerably over the last few decades and the latest generation of stoma appliances provides better patient comfort and a high degree of social convenience. Moreover, patients having a low anterior resection may suffer considerably from symptoms affecting their QoL although the problems are in many respects different from those in stoma patients. Therefore conclusions reached by previous QoL studies comparing stoma with non-stoma patients may no longer be valid. The question is therefore still whether – and if so to what extent – QoL benefits are to be gained by use of ultralow anastomosis compared with APR and a colostomy. What is the prevalence of physical, psychological, social and sexual dysfunction among patients whose sphincters have

been sacrificed compared with those in whom sphincters were preserved?

The results of a careful review of the literature on the subject have recently been published [21]. The Authors identified 25 potential studies. Eight of these – all non-randomised and representing 620 participants – met the inclusion criteria. Four trials found that patients having an APR did not have poorer QoL measures than patients with AR. One study found that the colostomy affected the patients' QoL only slightly. Three studies found that patients with an APR had significantly poorer QoL than after AR. Due to heterogeneity, meta-analysis of the included studies was not considered justified. The authors concluded that the results from the review did not allow firm conclusions as to the question of whether the QoL of patients after AR is superior to that of people after APR and suggested that larger, better designed and executed prospective studies are needed to answer this question.

Are There any Limitations for Advising a Low Anterior Resection and to Whom Should an APR be Recommended?

Most patients think of the stoma as a terrible disaster that might put an end to a normal life and many studies in the past have painted a gloomy picture of the stoma patient's lifestyle. Therefore the patient's personal preference would probably be for an operation that retains normal anal function, even at the price of functional imperfections and maybe even a somewhat reduced prospect of ultimate cure. But patients should know the shortcomings of each procedure. Patients have to know that with a properly sited and well constructed stoma, a perfectly fitted stoma appliance and the advice and support of a stoma nurse the patient will be able to lead a normal life. Patients should be informed that despite all precautions taken to avoid technical errors, the risk of anastomotic leaks and pelvic septic complications still remains a problem, particularly after low anastomosis; and the post-operative course is unpredictable. Patients have to know that such a complication may often be associated with a painful protracted post-operative course and a long hospital stay and that in some unfortunate cases the consequences may lead to rectal stump/pouch excision and eventually a permanent colostomy. Even with an uncomplicated post-operative course the functional result may be far from acceptable and quite a few patients will suffer from increased frequency, urgency, faecal incontinence, and permanent or occasional soiling. Although alternative neorectal constructions may improve function, they are demanding and risky procedures, they are still associated with functional imperfections, and it is doubtful if they will stand the test of the time.

Although the curative value and the radicality of the AR and APR are probably similar, the development of a local pelvic recurrence after a sphincter-saving operation is particularly distressing. The risk of pelvic recurrence may not be greater than after an APR, but a recurrence will give distressing symptoms at an earlier stage. The symptoms are more difficult to manage and may require another major operation, often at a time when the patient may just have recovered from the first operation, and this operation will seldom be curative.

Many experienced surgeons would probably advise against a low anterior resection for anaplastic tumours, and otherwise bulky and/or fixed tumours, reserving the operation for mainly local and limited growths, and those with low-grade malignancy. An APR may also be preferable for old age, particularly for those with a short life expectancy and those with a serious contemporary disease (diabetes, cardiac or pulmonary insufficiency etc.). In these patients an "ultralow" rectal resection – with square stapling of the anorectal remnant, omitting the perineal dissection – would be justified, considerably reducing the operative trauma and post-operative morbidity.

Considering the defecation urgency and imperfections of continence after an AR, it appears reasonable also to advise against the operation for immobile and bedridden patients i.e., for those who have difficulty reaching a toilet in time and for those who for their daily care are dependent on nursing staff.

Summary

Controversy still exists as regards the extent of lymphadenectomy, the use of the no-touch principle, the optimal free distal margin and importance of the irrigation/washout of the rectal stump in radical surgical treatment of rectum. There is in fact no statistical scientific evidence to support any of these measures for improving the oncological cure rate. Neither is there any scientific evidence to support the importance of TME or that an AR for a low sited rectal cancer does not compromise "radicality". Randomised controlled studies are lacking and it is doubtful – for ethical reasons – if such studies will ever be done. It would be virtually impossible to organise such a trial of two operations (one of which inflicts and the other avoids a permanent colostomy) because of the difficulty of getting patients to agree to enter a scheme that might leave them with an abdominal anus.

"There are two different ways to determine the best kind of treatment for colorectal cancer, the first

of which being the purely scientific way based on statistics and the second being a non-scientific way, the so-called 'gut feeling' decision, based on the question 'what operation would I myself prefer to undergo?'" [22].

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Rectal Cancer and Quality of Life

Gian Gaetano Delaini, Gianluca Colucci

Introduction

It is very difficult to divide epidemiological data of colon and rectal cancer as they are traditionally reported together. In 2002, there were 1 million new cases of colon and rectum cancer [1] (9.4% of the world total of new cancers). This means that it is fourth in incidence frequency in men and third in women. Among all large bowel tumours, rectal cancer accounts for about 30–40% of cases. Although the incidence is higher in developed countries, changes in environmental exposure, mainly dietary, have led to an increase in developing countries too. The high socioeconomic impact and increasing attention is easy understandable not only in the treatment but in prevention and early detection too, as demonstrated by the number of screening programmes developed.

The modern history of rectal cancer treatment began in 1908, when Miles [2] wrote "Method for performing abdominoperineal excision for carcinoma of the rectum and the terminal portion of the pelvic colon". This paper was the milestone of surgical treatment of rectal cancer and it was based on the concept of the "cylindrical spread of rectal cancer". Miles suggested that the location of the tumour in rectum was not important for the surgeon because only mutilating surgery (based on abdominal and perineal approach) could be an efficient treatment. The high impact of this kind of operation pushed surgeons into finding a new surgical approach.

In the 1940s, Dixon [3] described the anterior resection (AR) for rectal cancer, in order to avoid a definitive stoma, but the high incidence of technical failure and the lack of information about the biological history of cancer contributed to make the abdominoperineal procedure more popular than other procedures and it was not outdated for a long time. Only at the end of 1970s did the exponential growth in oncologic knowledge and technical devices begin to lead to dramatic change in the treatment of rectal cancer. First, the introduction of mechanical stapling devices overcame the technical problems of handsaw anastomosis at the distal rectum and anal canal. Also, the introduction of the "mesorectum" [4] concept (the milestone of rectal cancer behaviour) and the introduction of an efficient adjuvant and neoadjuvant therapy have dramatically reduced the incidence of Miles procedure.

Rectal surgery has shifted from the idea that "rectal surgery means permanent colostomy" to the new idea of surgery with sphincter saving, as there is a "consensus" that avoiding a permanent stoma is now generally regarded as favourable. This can be easily understood from the title of a recent review: "Do we still need a permanent colostomy in 21st century?" [5].

In our experience, as described in another chapter of the book, the introduction of triple neoadjuvant therapy (hyperthermia, radio- and chemotherapy) allows us to treat very low rectal cancer with a sphincter-saving procedure, but we do think that technical feasibility should not be the only parameter that surgeons consider when planning surgery.

The main end-points for judging the results of rectal surgery should include survival, recurrence and complication, but also quality of life (QoL).

Quality of Life Assessment

It is very difficult to define QoL, as it is a multidimensional construct. As poetically written by Mount and Scott [6], try to define QoL is like assessing the beauty of a rose: no matter how many measurements are made (for example size, smelling, colour), the full beauty of the rose is never captured. Having in mind this concept, it is easy to understand why, in the literature, there are many definitions of QoL:

- The extent to which hopes and ambitions are matched by experience [7].
- An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a wide-ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their

relationship to salient features of their environment [8].
- Appraisal of one's current state against some ideal [9].
- The things people regard as important in their life [10].
- An individual's sense of well-being in the somatic, emotional and social domains [11].

Even if we can presume the existence of some "universal features", QoL is an individual concept, which was born as an interaction between expectations, experience, social influence and pressure. Each of these points can weigh differently in different people. We can find patients heavily affected by health and functional problems that can report a better QoL than the general population. This was called the "disability paradox" by Albrecht and Devlieger [12]. Also, QoL is a dynamic concept that changes not only among people but also in the same individual and in different stages of life. Coping strategies are likely to change during life in response to ageing, stress and difficulties. For all these reasons, the first researchers felt like they were in front of the tower of Babel [13].

As will be discussed in more detail later in the chapter, researchers' efforts to create tests to measure QoL have been successful and there is a consensus among clinicians about which domains can be explored by QoL tests: physical, emotional, social and cognitive functions.

How to Test QoL

In the recent past, there was diffuse scepticism among researchers on using QoL tests in their trials or a trend towards using non-standardised questionnaires [14]. The former is due to the high number of methods for testing QoL: by interviews (structured, semi-structured, non-structured), by questionnaires (standardised, non-standardised) and by ad hoc questions. Theoretically speaking, most of them can be easily and efficiently used in clinical practice but as already explained, cannot be comparable and useful in a clinical research setting. In fact, the ideal instrument for achieving this target should have the following characteristics: able to analyse the four "important" domains, standardised, validated, easy to be completed and cross-cultural.

During the last 15 years, different kinds of questionnaires have been developed. They range from generic instruments, designed to test QoL in almost all kinds of patients, to specific for a particular kind of cancer. In the following, we briefly summarise these tests.

The SF-36 [15] and the EuroQoL instruments [16] represent generic health state index. They are well validated and are useful especially in testing QoL in chronically ill patients. They do not take into account specific problems for cancer patients and symptoms correlated to therapy.

The next reasonable step was to develop cancer-specific QoL questionnaires. So far, the most used cancer-specific questionnaires have been: the Rotterdam Symptoms Checklist (RSCL) [17], the Cancer Rehabilitation Evaluation System Short Form (CARES-SF) [18], the Functional Living Index-Cancer (FLIC) [19] and the European Organization for Research and Quality of Life Core 30 Questionnaire (EORTC QLC-C30) [20, 21].

The latter is, so far, the most widely used and validated questionnaire. The first studies started in 1986 and the final version was published in 1993. It is a multidimensional questionnaire, self-administrated and available in different languages. It contains 30 items that explore various aspect of QoL. In the fist part, the QLC-C30 explores "generic" and various aspects of QoL by five functional scales (role, emotional, physical, cognitive and social) and 3 symptom scales (fatigue, pain nausea and vomiting). In the second part, the influence of cancer-specific manifestations (such as sleep disturbance, financial impact of the disease, appetite loss) is analysed. The third part summarises the global results by two items on global health and QoL on a 7-point Likert scale.

The unique feature of this test is that it represents a "core instrument" for oncologic trials as it allows collection of a broad spectrum of information on all kinds of cancer patients. In fact, during the following years, the European Organization for Research and Treatment of Cancer developed detailed guidelines for creation of a new supplemental questionnaire [22, 23] to study the effect of particular types of cancer on QoL. Modules related to brain cancer [24], breast cancer [25] and lung cancer [26] were set up. In 1999, Sprangers et al. [27] published the Colorectal Cancer-specific Quality of Life Questionnaire Module (QLQ-CR38). It is structured as 38 items, employing the four category response options as the core instrument (QLC-C30). Nineteen questions are completed by all patients and they test function (body imagine, sexual functioning) and symptoms (micturition and gastrointestinal problems, chemotherapy side effects and weight loss). The other 19 are completed only by a subgroup and check sexual problems in male or female, defecation (only in patients with intact sphincter) or stoma-related problems (only in patients with stoma). In this way, the QLQ-CR38 explores symptoms and side effects of all different treatments for colorectal cancer (surgery with or without a temporary/permanent stoma, radio- and/or chemotherapy), becoming a tailored questionnaire for all rectal cancer patients.

In our experience, as in the literature, the QLQ-CR38 plus QLC-C30 can be easily completed by most of the patients without assistance, even if they have a low education level or old age. The average time to complete both tests is 12 minutes.

QoL: Research or Clinical Instrument?

As already stated, there is a diffuse resistance in using QoL assessment in surgical practice. Most surgeons believe they can be useful only for research, but even in this field QoL is an add-on rather than an internal part of most trials. There is a common perception among surgical oncology specialists that this parameter is useful, especially in the comparison of different therapies for advance stage disease where there are low chances of improving survival. In other words, the concept of "QoL" is strictly linked to palliative care.

Nowadays, evidence is accumulating to suggest that QoL *per se* plays a role as a prognostic factor. Baseline QoL predicts survival in different types of cancer, such as myeloma [28], head and neck cancer [29], breast cancer [30] and oesophageal carcinoma [31]. Also, two large cohort studies [32, 33] reached the same results by analysing different malignancies.

The first studies on rectal cancer obtained the same results. Earlam [34] demonstrated that a better QoL (measured by the Rotterdam Symptom Checklist Score) was associated with improved survival in patients with colorectal liver metastasis. Maisey et al. [35] retrospectively analysed patients with advanced colorectal cancer enrolled in 4 different clinical trials for testing different chemotherapy regimens. They found that baseline QoL was an independent prognostic indicator in all the patients involved in these four phase III clinical trials. Both previous studies take account of patients with advanced stage disease (inoperable cancer) and the QoL assessment was done only before therapeutic manoeuvres.

In 2001, Camilleri-Brennan et al. [36] published an interesting study where they analysed the change of QoL score among 65 patients undergoing curative surgical resection. They found two important far-reaching conclusions:

1. The QoL scores are dynamic and should be checked over time. A worsening in specific items could suggest the presence of specific problems (for example: loss in appetite can be associated with early bowel obstruction because of recurrence).
2. In their work, the combination of sociodemographic and QoL scores could predict 1-year survival with an accuracy of 76.8%.

Even if larger trials are needed to confirm these results, these conclusions are very important. Collecting information by routine use of QoL scores can help physicians to follow patients over time and plan treatment on specific areas affected by the disease. In our experience (unpublished data), weight loss and gastrointestinal symptoms (such as nausea and vomiting) are early predictors of tumour recurrence and, sometimes, they start 3–4 months before radiological finding or increase in neoplastic markers.

QoL and Stoma

Progress in neoadjuvant therapy and the use of mechanical staplers have led to a dramatic reduction in the number of abdominoperineal extirpations (APE) during the last 20 years. So far, whenever feasible, the golden standard in the treatment of rectal cancer is a sphincter-saving procedure such as AR. In many of the works in the literature, a definitive stoma is generally associated with a reduced QoL [37–40], with an increase in social isolation [41] and deterioration of body image.

In 2001, Grumann et al. [42] published a prospective study to evaluate QoL in patients undergoing APE or AR. For the first time, surprisingly, the Authors concluded that patients undergoing APE do not have a poorer QoL than patients undergoing AR. Also, after low AR, patients have a poorer QoL than after undergoing APE. Jess et al. [43] demonstrated that stoma influences QoL only slightly, while faecal incontinence after low AR can seriously affect QoL.

These data were partially confirmed by a recent Cochrane review [44]. Among 25 potential studies, Pachler included only eight of these (with 620 patients enrolled). It was claimed that it is not possible to come to the conclusion that QoL measures for stoma patients were poorer than for non-stoma patients.

The 4-year prospective study by Engel et al. [45] drew a completely different picture. Patients after APE had a lower overall QoL than after AR. Also, over time the scores improved only in AR and not in APE patients.

Moreover, Engel et al. took into account the problem of temporary stoma. The results of this study suggested that a stoma, even if temporary, affects QoL and the reversal of it can be one of the explanations of improvement in QoL scores in patients undergoing AR.

In our experience, we test anal sphincter function before planning surgery, especially in old patients or in patients with previous anal surgery. As reported in the literature [46], we do think that faecal incontinence can influence QoL more than the presence of a

stoma. Correct instructions about how to manage the stoma and how to perform colonic irrigation can reduce the problems connected to the presence of a stoma. As demonstrated by Hamashima [47], long-term QoL could be recognised according to the characteristics of rectal cancer patients, independent of the presence of a stoma.

Also, we think that a temporary stoma, especially in patients undergoing low AR with colonic J-pouch, can be useful. In our unit, these patients follow some training sessions (sometimes using pouch filling) in order to develop confidence in new perceptions and to increase sphincter tone in response to pouch distension. The stoma is usually reversed 60 days after surgery.

Bowel Dysfunction

These adverse effects after rectal cancer surgery on bowel function are related to sphincter or innervation damage [48] and the loss of rectal reservoir. The type of resection and the level of anastomosis may also play a role [49, 50]. Frequency of bowel motion, urgency, faecal leakage and incontinence are the most reported symptoms. Diarrhoea, constipation and flatus [51, 52] are also reported. Usually, these problems improve over time [53], but, especially in older patients, it can take a long time [54].

In stoma patients, there is much concern about flatus and foul odour [51, 55] but intensive pre-operative education about colostomy irrigation seems to reduce the incidence of these side effects.

The incidence of diarrhoea in patients with or without a stoma seems to be equal [55], while constipation is a more common problem in patients undergoing APE [45].

The introduction of a colonic J-pouch after low AR may improve the QoL of patients [56] by increasing the volume of the neo-rectum [57]. It decreases mean stool frequency without a rise in faecal incontinence or surgical complications [58]. The use of a temporary proximal diversion is preferred by many Authors [59].

Sexual and Urological Dysfunction

Sexual and urologic problems are common both in men and women after rectal cancer surgery, although they are more common in men. They are due to damage of pelvic autonomic nerves and pelvic floor sustained during rectal dissection [60]. The introduction of the TME technique with nerve-sparring technique has reduced the incidence of urological and sexual dysfunction [50].

Regarding the sexual sphere, in these patients it is very important (but sometimes it can be difficult) to distinguish problems due to anatomic damage from other symptoms linked to psychological disturbances because of depression, alteration of body perception and distress from the presence of a stoma. This evaluation permits us to help and improve the life of these patients with appropriate support. There are contradictory reports in the literature but it seems that patients' lives are likely to be beset by a poorly functional stoma or by a bad coping strategy more than the stoma *per se*.

The incidence of erectile and ejaculation dysfunction after surgery is reported to be very high after APE, ranging from 18 to 92% [40, 51, 61], while it is lower after AR (ranging from 9 to 30%) [45, 62, 63]. Loss of desire, diminished sexual activity and anorgasmia are also reported.

The prevalence of sexual problems in men seems to be higher in the elderly, but there is still debate about this, as it seems that, over time, older patients (>70 years old) recover continuously, while younger patient still complain of problems after 2 years [54].

Sexual problems in females are less investigated but cessation of intercourse, anorgasmia and dyspareunia are the most common problems [64]. The incidence of sexual dysfunction is higher after APE also in women.

The major urologic problems are incontinence, retention and dysuria. These are more commonly associated with APE than AR [65]. Supraradical lymphadenectomy affects urinary function in more than 30% of patients and in 20% of patients long-term use of a urinary catheter is needed [66].

Conclusions

The debate on QoL should not confuse the important topic of the correct management of rectal cancer, focusing evaluation only on patients rather than disease. First, it is very important to take care on primary end-points such as survival, disease free and tumour recurrence. Rectal cancer is a complex disease to deal with and it is clear that subspecialisation is becoming necessary. Subspecialty training in colorectal surgery and subsequent specialist board certification has a long tradition in the USA where the American Society of Colon and Rectal Surgeons was founded in 1899.

Hospital and surgeon's caseload are the key points for a successful outcome for patients, as uncorrected surgery is the first cause of high local recurrence rate [63, 67]. Porter et al. [68] stressed the importance of specific surgical competence and high caseload, as he demonstrated a higher risk of local recurrence in

patients operated on by low-caseload and non-colorectal-trained surgeons (hazard ratio for local recurrence of 4.29). As a direct consequence, there is a controversial debate about surgical training in rectal surgery [69, 70] as it is mandatory to offer the best treatment for all patients.

We do think that dedicated colorectal units represent the best way to manage this problem. In the experience of our team, a multidisciplinary approach is the golden standard. In dedicated and scheduled meetings, different specialists (surgeon, oncologist, radiologist, pathologist, WOC/ET nurses, psychologists) discuss cases and plan the patients' treatment. This approach guarantees a high level of care and increases the patients' compliance with suggested medical/surgical therapy. In fact, they feel involved in a good "curative project" and this reduces the stress of approaching the different specialists.

In these specialised colorectal units, QoL assessment can help physicians and should be inserted in patients' charts [71]. It can improve comprehension of patients' needs and expectations. Only in this way can every treatment be tailored to the patient and offer the best care for each patient.

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Mechanical Bowel Preparation (MBP) and Probiotic Administration Before Colorectal Surgery

Gerardo Mangiante, Annalisa Castelli, Birgit Feil

Introduction

Until now, mechanical bowel preparation (MBP) has been absolutely a dogma before colorectal surgery, as stated by Slim in 2004 [1]. However, MBP has been questioned during the last few years in many papers and especially in some meta-analysis published in the scientific literature. Some papers and reviews have stressed the uselessness of MBP. However, MBP is useful for cleaning the colon and removing firm faeces from the rectum both by oral laxative drugs, such as polyethyleneglycol, or by enema [2]. The advantage is easier management of viscus, and less possibility of outspreading faeces during surgery. Moreover, cleaning makes it easier to perform a colonoscopy if necessary, while reducing the hazard of damaging the colonic wall during laparoscopic surgery [3]. Also, the hazard of sepsis is reduced if a dehiscence of anastomosis occurs.

Disadvantages of the procedure are patient discomfort, such as nausea, swelling, bloating, dehydration and electrolyte disturbances, and a higher social cost for these drugs. Already more than 30 years ago a randomised trial questioned this issue [4], and during the last 10 years many trials and some meta-analysis has demonstrated the uselessness of MBP for prevention of septic complications and anastomosis dehiscence onset.

MBP and New Knowledge on Colonic Physiology

MBP is founded on three rules:

1. absolute starvation, especially of fibre;
2. antibiotic prophylaxis;
3. enemas and/or laxative drugs.

One of the last papers on this topic was by Platell and Hall [5], questioning MBP in "Colon and rectum disease" in 1998 [6]. Then many papers in the international literature focused on this argument, especially in the last three years [7–10]. All have stated that MBP is more harmful than useful.

The landmark was a deeper knowledge of the physiology of the colon and its power in finding energy for the body [10]. Really, the viscus is not only able to concentrate water and rescue sodium, but also produces energy for the whole body by producing short-chain fatty acids (SCFA) from the fermentation of food fibres.

The effects of SCFA are concentration dependent. Low doses stimulate motility, while high doses inhibit contractions of the loops [11]. Moreover, SCFA stimulate secretion of gastrointestinal peptides to modulate peristaltic waves [12]. SCFA increase microcirculation of the colon and distal ileum, where the large amount of anaerobes produce SCFA by fermentation [11]. SCFA are mainly produced in the colon and also stimulate mucosal blood flow in the rectum of patients who have undergone Hartmann's procedure [11]. It must be kept in mind that microcirculatory failure seems to be the main determining factor of anastomosis failure. After production by fermentation, SCFA are readily transported across colonic epithelium [11–13]. So, deprivation of fibre should be detrimental to colonic cells [12].

Fermentation by endogenous bacteria is really the second digestive system of our body. Really, man has two separate digestive systems, one based on digestion by enteric cells of the gut, and another much more complex one based on fermentation by digestion of bacteria. The bacteria are so important that we can call them the "microbe organ". Energy [14] from fermentation produces SCFA and it is more than 8% of the whole daily production of energy of the body.

SCFA are propionic, acetic and butyric acid. Butyric acid is the real fuel of Bifidobacteria and is absorbed at 90% by the colonic cells. These agents could have a protective effect against leakage of anastomosis, enhancing vascularisation and protecting the anastomosis from leakage as failure of microcirculation is caused by this complication [15].

Of extreme interest are the patterns of deprivation colitis found on colon segments without nutrients for many months, such as after dehiscence of colocolonic anastomosis and performance of ileostomy [16]. The disease is caused by deprivation of nutri-

ents to the colonic mucosa [10]. So, we have to understand that nutrient delivery should be continuous to improve adequate blood supply and energy production to the mucosal cells [10].

On Burke et al.'s [17] evidence, MBP did not influence the outcome in 2 groups of patients (with and without) submitted to ultra-low anterior rectal resection. In 1998 Platell and Hall [5] performed a meta-analysis of this issue. MBP seems to reduce only wound infection onset. Jansen et al. [8] stated MBP could safely be omitted for right colonic resections, but not antibiotic drugs as prophylaxis of wound infection.

Van Geldere et al. [6] did not find any benefit with the use of MBP on colonic surgery in a trial of 185 patients. Zmora et al. [7] in 380 patients treated by colonic-rectal surgery, found that MBP has to be performed only in the presence of a small (<3 cm) tumour that could not be seen on a perioperative colonscopy. Whilst Zmora and co-workers again, in a last specific review, found no data in support of MBP on colonic sugery [7].

Also, diet restriction is questionable as physiology has shown that faeces are made up of only 5–7% food, while the majority is bacteria, apoptotic enteric cells and mucous. Mucous is the main part of the intestinal barrier and one of the most important weapons against bacterial translocation. It is made up of embedded immunologic cells from lamina propria and mucosal lymphocytes. Therefore, it would be illogical to destroy it by aggressive oral preparation or by enemas.

Slim et al. [1], late in 2004, suggested that MBP using polyethyleneglycol should be omitted before colorectal surgery. Anyway, the presence of hard faeces on left segments of the colon and rectum obstruct surgical procedures.

Kehlet [18] and Basse et al. [19] suggest performing an enema as the surgeon prefers for cleaning the rectum and the colon before resection.

Ljungqvist [20] in 2005 gave up bowel preparation for colon resections, but still use it for rectal resections. In their experience this procedure works fine, without any true benefit for laparoscopic resections for colon or rectum. For the former, this group have patients ready to leave the hospital 2–4 days after rectal surgery and 4–6 days after open surgery using small incisions as best possible. For a right-sided hemi-colectomy the incision is almost the same as in laparoscopic surgery.

Excessively strong enemas could destroy the mucus layer on the rectal and colonic mucosa, and this layer is full of IgA and probiotic bacteria.

Probiotic Agents on Colorectal Physiology

On nutrition, probiotics are nutritional supplements containing living micro-organisms, e.g., bacteria or yeasts, that have a beneficial impact on the host by improving the endogenous flora when introduced to a human being. And we can expect that prophylactic treatment such as MBP with these agents or a real antimicrobial interference therapy on surgical practice.

Some series in surgical clinics, especially in liver transplantation, are encouraging [21]. In inflammatory bowel diseases such as ulcerative colitis after proctocolectomy, administration of probiotics avoids recurrence of pouchitis and shows excellent results in minimising the recurrence of this dismal complication [22].

Unfortunately, until now we have not known the true power of these agents, their safety, their power against other micro-organisms, their immunologic charge, etc. But in the future we are sure that probiotics should be one of the most important strategies against the main threat of surgery, the onset of infection.

Closing Remarks

The papers on this topic until now have been too few. Danish experience [18] on fast track surgery reported sigmoid surgery more than rectal surgery. However, in rectal surgery many Authors have spoken out against aggressive preparation of the bowel, and the so-called fibre-free diet. Antibiotic prophylactic administration only aids in reducing wound infection. Actually, the way forward is to reduce the strict rules of MBP, even if we have to obtain deeper information on this topic. Safeguarding the colonic environment could be the weapon to obtain the best result in this surgery.

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Indications for Local Excision in Rectal Cancer Surgery

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Introduction

Local excision (LE) with or without chemoradiotherapy represents an alternative treatment to major radical surgery in small low rectal cancer. LE can be used in selected cases with the advantages of lower morbidity and mortality, maintaining at the same time a good functional result. On the other hand, from the literature some concern emerges on the higher rate of recurrence and the possible compromise of the potentials of cure a radical rectal resection would offer. The key to a successful LE is certainly a reliable pre-operative staging and the correct selection of patients. The criteria of eligibility for curative LE are still a matter of discussion and are not generally accepted. In this chapter more useful pre-operative staging tools are analysed in detail, some therapeutic strategies are presented and finally, as to date no guideline has been fully agreed upon, current recommendations for curative and palliative LE are discussed.

Pre-Operative Staging and Patient Selection

The staging system adopted in the present chapter refers to TNM classification [1]. Stage T1 has been divided into three subgroups according to the Japanese classification (Fig. 1).

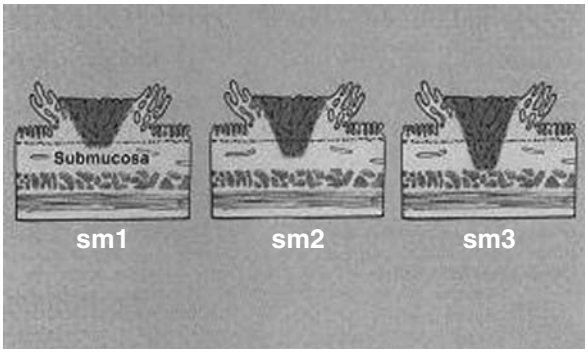

Fig. 1. Depth of invasion into the submucosa: *sm1*, upper-third; *sm2*, middle-third; *sm3*, lower-third (With permission from [8])

Only N0 tumours are amenable to undergo LE of low-lying rectal cancer because by definition satellite lymph nodes are left behind [2]. Considering this aspect, a correct and reliable pre-operative staging is of dramatic importance [3]. Besides, should LE fail, salvage rectal resection remains the only chance, although prognosis remains poor in these cases.

In order to assess nodal involvement, the following predictive factors have been analysed: tumour depth (T), age, lymphovascular invasion, unfavourable histology, grading, tumour morphology and size.

Tumour Depth

In the majority of studies, depth of tumour invasion through the rectal wall is considered the most important independent prognostic factor for nodal involvement. As a matter of fact the risk for N+ has been estimated from 0 to13% in T1, 12–28% in T2 and 36–79% in T3 and T4 [2, 4, 5]. Kikuchi et al. [6] have divided T1 tumours into 3 subgroups according to the level of submucosal invasion. T1sm1 stands for slight submucosal layer infiltration, T1sm2 for intermediate infiltration and T1sm3 for whole thickness submucosa involvement [6–8]. The T1sm3 subgroup bears a risk of lymph node metastasis estimated from 20 to 27%; this represents a contraindication to curative LE.

Age

Although age is not an independent factor for nodal involvement, Sitzler et al., in a study on 805 patients all treated with radical rectal resection for rectal cancer, compared groups with the same T staging but different age, showing that the risk of nodal involvement was much higher in the patient groups younger than 45 years old (N+ being 33.3% in T1 subgroup) [9].

Lymphovascular Invasion

The predictive value of lymphovascular invasion is still debated, although the majority of Authors consider this element as indicative of poorer outcome [10]. In a Japanese study on 182 patients lymphovascular invasion has been detected in 30% of T1sm1, though no one in this group showed lymph node invasion. The Authors concluded that the degree of infiltration through the rectal wall was by far a more reliable predictive factor than lymphovascular invasion [6]. Nivatvongs, reviewing 81 cases of degenerated colorectal polyps, showed vascular and lymphatic invasion in 37% and 20% of cases respectively, concluding that as far as it is carefully looked for, lymphovascular invasion seems a rather common finding in early rectal cancer [7]. On the other hand, Sengupta and Tjandra reporter a paper by Brodsky et al., which, although in a small group of 24 patients, showed that in T1 rectal cancer signs of lymphatic invasion imply a 33% of nodal involvement compared to 0% of N+ when no sign of lymphovascular invasion is present [2]. In a more recent study on 353 T1 rectal cancers, Nascimbeni et al. both in a univariate and a multivariate analysis concluded that lymphovascular invasion is one of the three unique predictive factors of nodal involvement, with a high grade of statistical significance (p=0.005) [8].

Unfavourable Histology

The presence of budding (islets of focal dedifferentiated cancer) at the invasive front or signs of signet-ring-cell adenocarcinoma, or both elements, are histopathologic findings referred to as unfavourable histology, bearing a higher risk of nodal involvement and ultimately of adverse outcome, as evidenced in some recent Japanese works [11–13]. Masaki et al. reported unfavourable histology to be the only prognostic factor significantly related to lymph node metastasis in T1 and T2 rectal carcinoma undergoing LE or radical surgery [13].

Grading

The predictive value of grading relevant to nodal invasion is controversial. Although a less differentiated cancer theoretically metastasises more easily to regional lymph node and distant organs compared to a well differentiated one, statistically significant data supporting this concept have been observed in univariate analysis only [8]. Hase et al. [14] showed how the risk of nodal metastasis increased in those cancers with evidence of undifferentiated histology at the front margin compared to those in which an undifferentiated component was detected within the neoplastic mass. In his paper Kikuchi notes that among 64 patients with T1sm1 no one developed local recurrence or lymph node metastasis although 12.5% of cases have been diagnosed a poorly differentiated lesion [6].

Tumour Morphology and Size

Many studies demonstrated that both morphology and size of the lesion do not represent independent prognostic factors for nodal involvement [9, 10]. The diameter of the lesion is nevertheless important when considering LE, as lesions wider than 3–4 cm leave a wide defect in the rectal wall that might lead to rectal stenosis [2, 15].

Pre-Operative Local Staging Assessment

An accurate pre-operative staging of rectal cancer is of dramatic importance for successful local treatment. Digital examination, endorectal ultrasonography (EUS), magnetic resonance imaging (MRI) and computed tomographic scanning (CT) are all valuable tools that play an important role in the staging process of rectal malignancies, and basically help identifying those patients who should be treated by radical resection, those amenable to LE, and those in whom neoadjuvant radiation and chemotherapy should be recommended first.

Digital Examination

Until recently, digital examination was the most important and useful tool in assessing a rectal cancer. It allows precise information on the location of the lesion, size and fixity that, where present, suggests a locally advanced tumour [16, 17]. The diagnostic accuracy of digital examination for T-stage has been estimated around 62–83% when carried out by an experienced surgeon [2, 17, 18] and somewhere around 44–78% for less experienced ones. Digital examination is definitely less accurate for the assessment of N-stage, with figures that do not exceed 67% in experienced hands [2].

EUS

During the last decade EUS has been increasingly used to evaluate lesions lying in the last 10–12 cm of rectum from the anal verge. Basically it is a morphologic study of the rectal wall with its mucosal, submu-

cosal and muscular layers, visualised as a classic 5-layer echoic pattern (or a 7-layer pattern if a 10-MHz probe is used). Cancer usually appears as a hypoechoic lesion invading one or more echoic layers through the rectal wall. Accuracy for T-stage has been reported in the literature from 67 to 95%, with a sensitivity of 83–98%, specificity 75–87%, ppv 89 and npv 95 [10, 16, 17, 19]. Pitfalls involve the operator's experience, the degree of tumour infiltration and some technical issues such as artefacts, peritumoral inflammation and post-biopsy alteration of the echoic pattern. Artefacts are generated by the presence of air bubbles between the rectal wall and the probe, causing a complete loss of signal or by the position of the probe with respect to the bowel wall or lesion. If not visualised at right angles, layers of different echogenic property appear thicker at their interface until a mirror image is generated. Peritumoral inflammation appears as a hypoechoic band at the infiltration margin that can be easily confused with the true level of infiltration, negatively impacting T-stage. Peritumoral inflammation is the main cause of overstaging, especially in T2 cancers [20]. EUS is rather inaccurate for N-staging mainly because morphologic and echogenic characteristics of lymph nodes alone are not sufficient to clearly assess possible lymph node positivity and also because lymph nodes other than those located in the mesorectum are out of the reach of the rigid probe [16]. As a matter of fact accuracy figures varying from 61 to 83% [10, 17] are reported in the literature, with a sensitivity as low as 33%, and a specificity of 82% [3]. N-stage accuracy can be increased by echo-guided lymph node needle biopsy performed during the examination [21], but further works are necessary to address the benefits and pitfalls of this promising technique.

EUS is at present the most accurate technique for pre-operative local staging of rectal cancer, as confirmed in a recent meta-analysis [22] that compared EUS with MRI and TC (Table 1).

MRI

The increasing interest in the circumferential resection margin (CRM) (Fig. 2), whose prognostic value is considered by some Authors to be superior to T-stage [16, 23], and the introduction of more powerful coils up to 1.5 Tesla, have drawn new attention to MRI.

Average figures of accuracy are around 66–82% for T-stage and 60–72% for N-stage and do not differ much from those obtained with EUS, but as evidenced by Bipat et al. [22], MRI allows an accurate evaluation of the CRM. For when N-stage is concerned, the recent introduction of new contrast agents such as utrasmall superparamagnetic iron oxide (USPIO) seems promising for the diagnosis of positive lymph nodes. This agent is captured by macrophage cells in the reticulo-endothelial system of normal lymph nodes, while metastatic lymph nodes are incapable of taking USPIO as the reticulo-

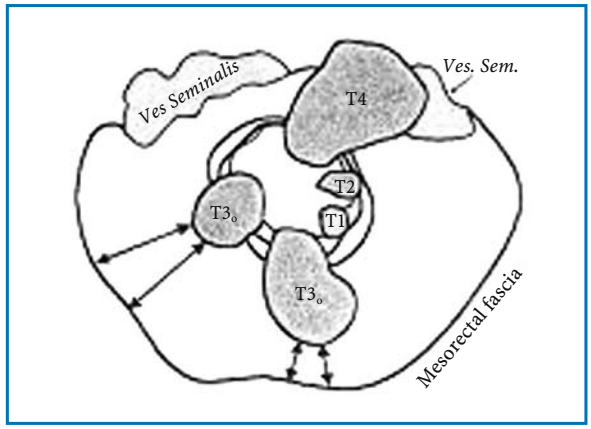

Fig. 2. The circumferential resection margin (CRM) (with permission from [23])

Table 1. EUS, CT and MRI: pre-operative staging accuracy for rectal cancer (Modified from [22])

Stage	Imaging modality	Sensitivity (%)	Specificity (%)
Muscularis propria invasion	EUS	94	86
	CT	NA	NA
	MR	94	69
Perirectal tissue invasion	EUS	90	75
	CT	79	78
	MR	82	76
Adjacent organ invasion	EUS	70	97
	CT	72	96
	MR	74	96
Lymph node involvement	EUS	67	78
	CT	55	74
	MR	66	76

endothelial system is altered to some extent [23]. Although promising, this new technique needs further validation.

CT Scan

Since the introduction of EUS that shows all the layers of the rectal wall, the role of CT scan in local staging has been limited. It remains the most important exam for the detection of distant metastasis.

Therapeutic Strategies

Once local and general staging have been completed, the decision to proceed with a curative LE should be taken after evaluating other important aspects (Fig. 3) such as the size of the lesion, its position in the rectum, the functional status of the anal sphincters, and the route the surgeon intends to follow: either transsacral, trans-sphincteric or transanal. The advantage of LE over other local treatments is that the lesion can be retrieved at the end of the operation for thorough histological examination, allowing for further treatments should any adverse factor come up [10].

In the literature, local recurrence after curative LE is reported from 0 to 18% in T1 cancers and from 11 to 47% in T2, compared to 4–30% local recurrence after radical rectal resection [2, 5, 10]. Mellgren et al., comparing the results of LE with respect to radical rectal resection showed 18% of local recurrence in T1 patients and survival rate significantly reduced in T2 after LE compared to radical surgery (65 vs. 81%), concluding that curative LE is contraindicated for T2 cancers, while in T1 there is a high risk of recurrence [5].

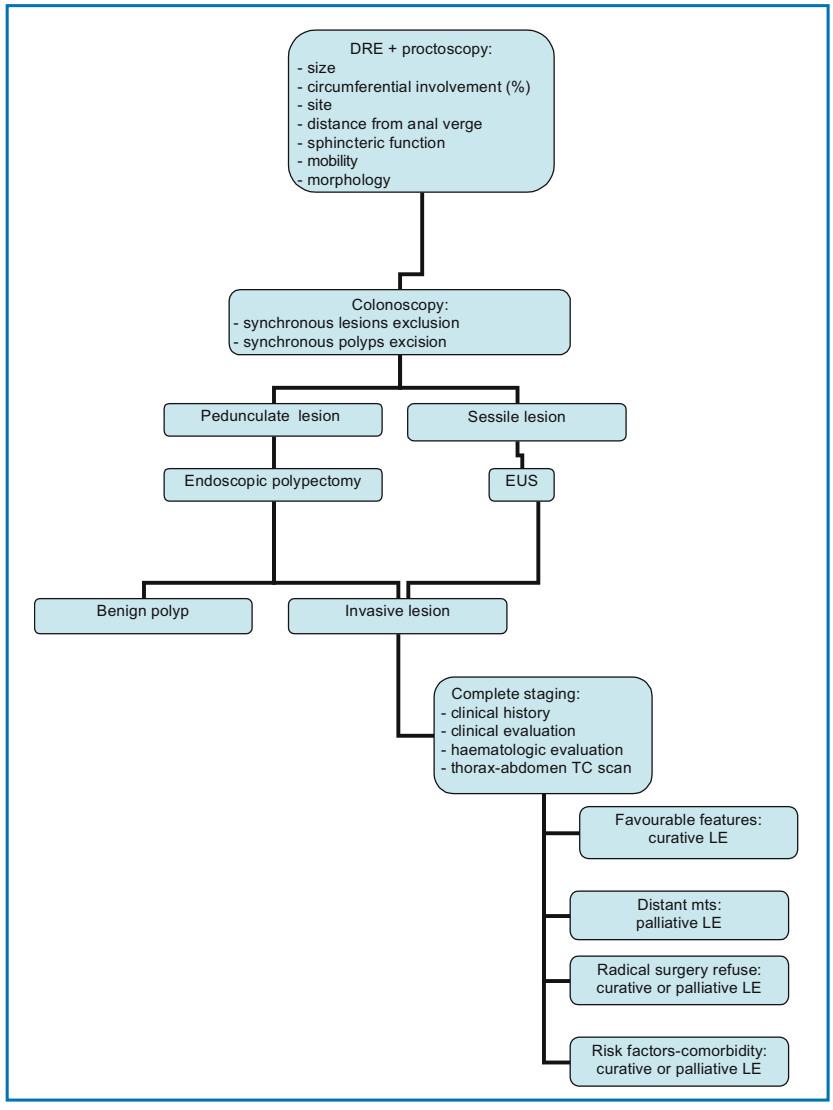

Fig. 3. Clinical evaluation flowchart

Both short- and long-term results seem unsatisfactory when surgical margins are involved, in cases of poor histology and when lymphovascular infiltration is present. In these cases the majority of Authors suggest an immediate radical rectal resection, with long-term results substantially similar to those after primary rectal resection. On the contrary, long-term results after salvage surgery, carried out only after the recurrence has occurred, are very poor. In fact, 5-year disease-free survival after immediate radical surgery is 94.1% *vs.* 55.5% after salvage surgery [2, 5, 24, 25]. The biological behaviour of the recurrence is probably different after LE and after rectal resection because in the former case the recurrence is related to the bowel wall, while in the latter it is related to the pelvis. As a matter of fact salvage surgery for recurrence after LE is higher with respect to salvage surgery after abdomino-perineal resection or anterior rectal resection [2]. Hershman et al. in a recent study on long-term results after LE [26], sustain that local recurrence rates are unacceptably high, with mortality rates that worsen with time as evidenced in 10-years, follow up, and advise against LE as a curative procedure.

Current Recommendations

On the basis of what has been presented before, curative LE should be considered in very select cases. In Table 2 the selection criteria for LE of rectal cancer are summarised [10].

In patients undergoing excision of a malignant polyp level 1, 2 or 3 according to Haggitt's classification [27], with a disease-free margin of a least 2 mm, the risk of local recurrence is probably less than 1%, even if lymphovascular infiltration or low-grade differentiation have been detected. In these cases a major surgical procedure is not justified. For T1 cancers, Haggitt's level 4, the risk of residual cancer or lymph node metastasis depends on the level of submucosal infiltration. In T1sm1 with favourable histology the risk does not exceed 1–2%, a figure equivalent to perioperative mortality after anterior resection in low-risk patients. In these cases LE can be considered an adequate procedure. For T1sm2 with favourable histology the risk of residual cancer or nodal invasion grows to 2–10%, so if the patient has a low operative risk an anterior rectal resection would probably be the best choice, leaving LE for patients in a poor general condition or with moderate–high operative risk. In cases of T1sm2 with unfavourable histology, anterior rectal resection should be considered, or alternatively an adjuvant therapy if LE has already been carried out.

LE is not indicated in T1sm3. In T2 where the patient's general condition does not allow a radical resection, neoadjuvant radiotherapy followed by LE

Table 2. Selection criteria for rectal cancers suitable for local treatment (Modified with permission from [10])

- Accessible
- Amenable to complete excision
- Haggitt levels 1, 2 or 3 in pedunculate polyps (clear margin ≥ 2 mm)
- Haggitt level 4 (pedunculate or sessile T1 cancer) with sm1 invasion
- Haggitt level 4 (pedunculate or sessile T1 cancer) with sm2 invasion
  well or moderately differentiated
  no lymphovascular invasion

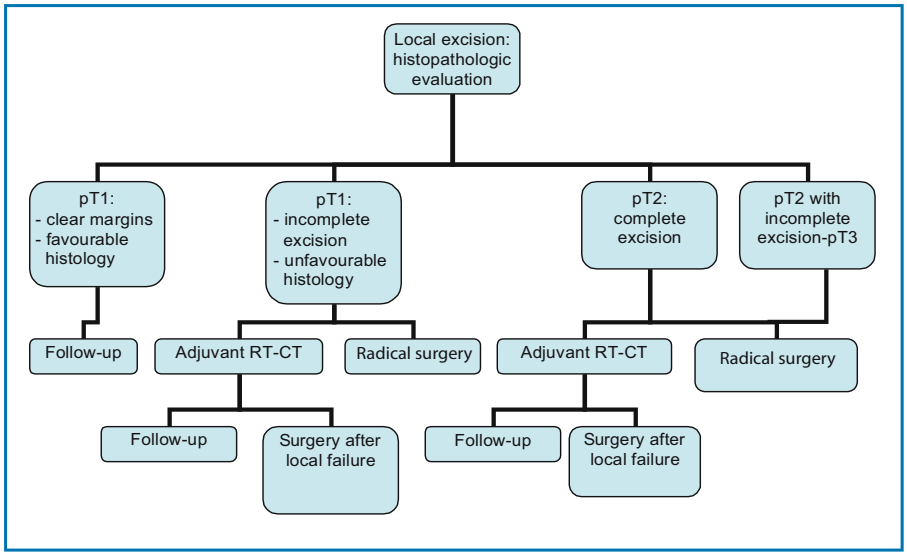

Fig. 4. Flow-chart on decision making after local excision

can be considered, together with other adjuvant therapies [10].

Finally, LE can be offered to patients not eligible for major surgery or who refuse to undergo a major operation. In these cases a multimodal approach with neoadjuvant or adjuvant radiochemotherapy is usually adopted [28] (Fig. 4).

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Local Excision of Rectal Cancer: TEM

Tomaš Skricka

Introduction

Minimally invasive treatments or operations preserving sphincter functions are indicated for rectal polyps, rectal carcinoma *in situ* and low stages of rectal cancer. Local excision of rectal cancer is feasible in only a highly select group of patients. As for our experiences, less than 4–6% of all rectal cancers are amenable to local excision. Only those tumours that involve the mucosa and submucosa and that have not extended beyond lamina propria are suitable. Furthermore, only those tumours that are less than 12–20 mm in diameter are appropriate. It is important to remember that if there is any doubt whatsoever about nodal metastases, it is far wiser to embark on a radical rectal excision than to attempt complete cure by local excision and fail. This is particularly relevant now that sphincter-saving resections are feasible and are relatively easy to perform in these cases. The only exception to this philosophy is the patient in whom a radical rectal excision might be contraindicated because of coexisting disease. These tumours must be very carefully assessed pre-operatively and the precise location within the rectum determined. Intrarectal ultrasonography is particularly valuable in identifying T1 and T2 tumours. Information about the upper extent of the lesion is crucial because lesions with an upper margin more than 8–9 cm from the anal verge are unsuitable for local or transanal procedures. Anteriorly placed lesions are best managed with the patient in the prone jack-knife position. Posterior lesions are best managed with the patient in the lithotomy position, although admittedly those lesions lying just beyond the anorectal angle can prove quite difficult to remove peri-anally with the patient in this position. The mobility of the tumour in the submucosal plane should be also assessed. Mobile tumours can usually be delivered into the operating field by placing six to eight sutures around the periphery of the tumour, leaving the suture tails long and then gathering the tails together in a manner resembling the cords of a parachute, twisting them and pulling the lesion *en masse* into the operating field.

Our recent treatment scale of tumour local excision is quite wide:

Polyps

Intrarectal Polypectomy

The patient is prepared for the bowel operation with conventional mechanical bowel preparation. Polypectomy is then undertaken with an insulated coloscope and a loop diathermy snare. Once the neck of the polyp has been grasped by the snare, the current is applied and the polyp is excised and retrieved. After the procedure, careful attention must be paid to the diathermised stalk to ensure that there is no bleeding and that the rectal wall has not been tended; a situation that might result in rectal perforation unless the base of the polyp is properly inspected. This procedure is indicated in polyps situated in rectum from 5 cm up to 15–18 cm. The diameter of the polyp should not be larger than 5 mm.

Transanal Polypectomy

The operating anoscope (Fig. 1) is introduced and the polyp is identified. The base of the polyp is infiltrated with a weak epinephrine solution (1:300 000) so that the mucosa is lifted off the submucosa. A 1-cm margin around the polyp is included in the excision, particularly for villous lesions, so that the entire mucosa and polypoidal lesion are excised, leaving a bare rectal wall at the base. A polyp that cannot be easily excised in the plane suggests malignant invasion, in which case the operation should be immediately converted to a full disc excision of the lesion.

Surgical procedures in the rectum, such as resection of sessile polyps, have mainly been performed with the use of retractors. Surgical manipulation inside the rectal cavity using retractors has its disadvantages. The surgical view is restricted to the area between the branches of the retractors, the blades of

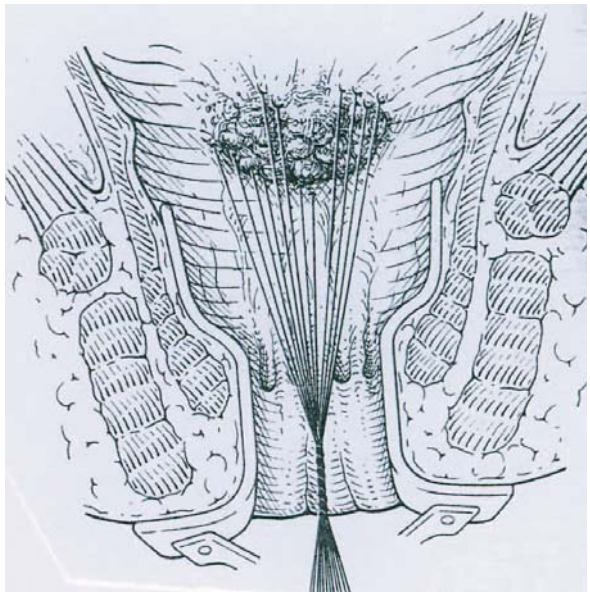

Fig. 1. Transrectal polypectomy technique

the retractor obstruct parts of the rectum, and the area located higher than the retractor tends to collapse, again obstructing the view. The surgical instruments and the hands of the surgeon restrict the direct vision of the operating field. For these reasons, transanal surgical procedures have been mostly applied for lesions in the lower third of rectum.

Depending on each situation, parts of the tumour-bearing area of the rectum can be prolapsed towards the anal verge, thereby utilising the standard technique in most cases up to 7–8 cm from the anal verge.

Early Cancer and Selected Cancer Cases

Objectives in rectal cancer surgery:
- prevention of surgical morbidity/mortality
- optimal oncological clearance
- prevention of local recurrence
- quality of life

Patient selection:
- elderly, frail and high anaesthetic risk
- patient refusal of a stoma or radical surgical treatment

Schema–Algorithm: See the Chapter Dealing With the Indications

Ablative procedures:
- electrocoagulation
- laser vaporisation
- cryodestruction

are used mostly as palliation in cases where a more appropriate method is contraindicated. There is no cancer tissue selection, 20% secondary haemorrhages and poor clinical outcome.

Endocavitary Radiation (Papillon)

The principle of this method is direct contact radiation of 100–120 Gy. This method is also used mostly in palliative settings, but in selected cases there is a 5-year local control of 76–90% (T1–T2 tumours).

Perianal Technique for Selected Cases of Early Rectal Cancer

High recurrence rates – T1 18%, T2 47% – are described in all of these approaches, and survival varies in T1 from 72 to 90% and in T2 tumours from 55 to 78%.

A number of different methods are currently available for the treatment of rectal tumours. Anterior resection or abdominoperineal resection with total or proximal mesorectal excision is the gold standard for rectal cancer, as these methods offer the best chance of cure. Perianal local resection under direct vision may be an appropriate alternative for patients with early rectal cancer who are unfit for major resectional surgery and is the treatment of choice for rectal adenomas that are too large for coloscopic excision. Advantages of this technique are the avoidance of the significant morbidity and mortality of major surgery, avoidance of stoma and a short hospital stay. After local excision patients may still receive adjuvant therapy when necessary and proctectomy remains an option for local recurrences or excised lesions that show unfavourable pathology. Alternatives to perianal local resection include transanal endoscopic microsurgery (TEM), Mason's technique of trans-sphincteric approach and Salvati's method of transanal resection.

The beginning of the intervention does not differ from that of transanal polypectomy. A series of sutures are placed around the periphery of the tumour, as just described. The excision should include at least 2 cm from the macroscopic edge of the tumour to ensure complete removal of tumour. The mucosa and submucosa are divided peripherally around the lesion using diathermy. All submucosal vessels must be secured during division of the mucosa and submucosa in order to maintain a dry field. If the tumour has been correctly staged, complete clearance can be achieved by excision of a disc of full-thickness rectal wall. Indeed, if perirectal fat is not observed, the excision has not been sufficiently deep to achieve adequa-

te clearance. It is often helpful to place a series of stay sutures beyond the resection margin to facilitate the closure of the defect once the tumour has been removed. Once the lesion has been removed completely, the defect in the rectal muscle should be closed transversely using continuous resorbable monofilament suture 2/0. The mucosa is closed with a running resorbable monofilament suture 3/0.

Posterior Parasacral Rectotomy

Posterior parasacral rectotomy has been widely used for larger lesions of rectum higher than 5–8 cm from the anal verge. We used parasacral incision and resection of segments 4–5 of the sacrum and the coccygis (Localio et al. [1], which is modified Kraske operation [2]). A longitudinal incision of the rectum was made between pursestring sutures, leaving intact the external sphincter muscle and the puborectal muscle. This procedure is rarely performed today.

Trans-Sphincteric Approach [3]

Most higher rectal lesions would be treated today by total rectal excision and a low anterior resection or colo-anal anastomosis. Nevertheless, in a few selected cases trans-sphincteric excision may be useful.

The patient is placed in an appropriate position, depending on the localisation of the tumour. We made a parasacral incision caudally. The peripheral aspect of the incision is deepened to identify the lower fibres of gluteus maximus. Then the somatic and visceral musculature around the anorectum is subsequently divided longitudinally, marking the internal anal sphincter and mucosa separately for subsequent reconstruction. The rectal lesion should then be displayed. Essentially the same technique is used, as described previously for tumour excision, ensuring that a full-thickness disc of rectal wall is removed with the lesion. The rectal wall is then closed transversely in two layers. The anorectum is reconstructed by closure of the mucosa, then the internal anal sphincter and finally the external anal sphincter. Skin closure completes the operation.

This operation barely has a place in the treatment of rectal cancer any longer, but in very special cases it may play a role.

Rectal Polypectomy by Transanal Endoscopic Microsurgery (TEM)

TEM is a recognised, minimally invasive operative technique for clear view resection of tumours in the rectum [4, 5]. Rigid rectoscopy is one of the oldest techniques in endoscopy of the intestinal tract. New techniques were developed with more advanced optics in the beginning of the last century [6]. Interventional procedures through rigid rectoscopes under gas dilatation had been limited to simple procedures such as snare resections. Operative rectoscopes were developed with diameters up to 4 cm, but were used only as mechanical retractors and conventional instruments were applied for minor surgical procedures inside the rectal cavity.

The Operative Rectoscope and the Instruments

The operative rectoscope is 40 mm in diameter, which compromises the acceptable limit of dilatating the anal sphincter and adequate space inside the tube to perform complex surgery. Two different tubes are available with either a length of 10 or 20 cm. At the distal end, the rectoscope tubes have a 45° angle (Fig. 2). The tubes are introduced into the handpiece. The handpiece allows introduction of the operative rectoscope with the respective obturator for endoscopic examination of the rectum using the glass window. A cold light adapter is integrated into the glass window for optimal illumination during examination. In preparation for the procedure, the handpiece is connected to a holding device, mounted to the rail of the operating table (Fig. 3). A special arm belongs to the operative system. A double-ball joint allows easy adjustment of the rectoscope and optimal handling during the operation. During the actual procedure, the working insert is used. In our recent model, single flexible tubes are adjusted to the working insert to allow sealing during insufflation. The flap seals are integrated as well to prevent gas leakage during instrument removal. This model also allows performance of haemostasis with conventional instrumentation, if needed.

The instruments for TEM are designed specifically because the relatively narrow tube of the rectoscope limits manoeuvrability of instrumentation [7]. Therefore, a bayonet-type angulation has been introduced into the system that allows a wider working area, compared with straight instruments. Figure 4 demonstrates the angular instruments that provide a longer distance between the optic and the working field. Specific technical details have been integrated into the needle holder. A small upper jaw fixes the needle in place, while the broader excavated lower jaw brings the needle into an upright position.

The curves in the suction device allow the assistant to guide the suction tube in case of bleeding without extensive mechanical conflict with the operative instruments of the surgeon. The forceps perform two

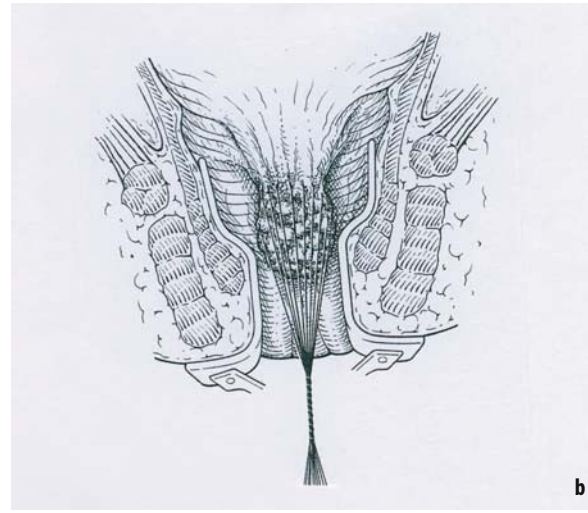

Fig. 2a, b. Operative rectoscope

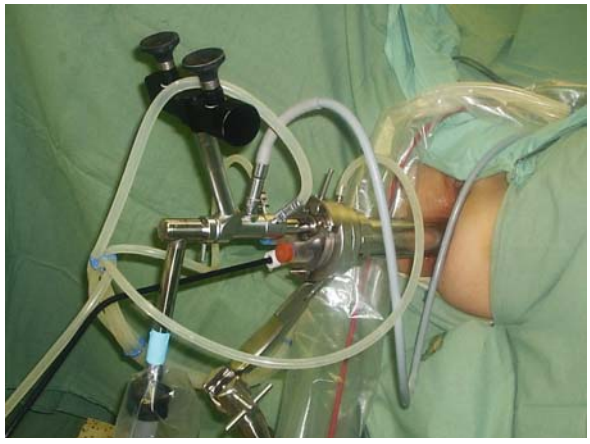

Fig. 3. Operative rectoscope mounted to the operating table rail

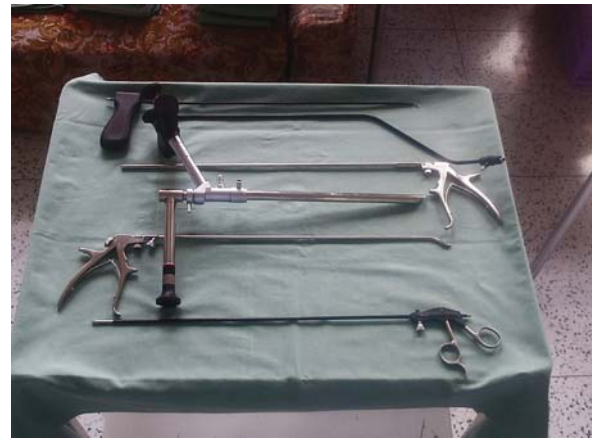

Fig. 4. Angular instruments for TEM

different functions. The tip excavations allow safe grasping of the tissue. The jaws are flat so that the needle can be grasped during the suturing process. A silver clip with a central cut is used. Instead of the knotting process a monofilament thread is placed into the central cut, tensed and the clip is fixed to act as a knot substitute.

The Stereoscopic Optic

During the dissection process and during the suturing, precise manipulation of two instruments is mandatory. Monocular vision provides less precise information because of the parallel movement of the instruments. Subsequently, the triangulation effect that provides spatial information is not available. The optical system provides a natural stereoscopic view in combination with a high-resolution image. A third rod lens optic has been introduced into the stereoscopic optic that is connected to a video camera. Images are displayed on a screen to provide useful information to the entire operative team and for teaching purposes.

By means of TEM, together with optimal coagulation systems, it is possible to provide mucosectomy, partial or full wall excision and segment resection, with preservation of an adequate safety margin between the tumour and the line of resection.

The most frequent indications of TEM are as follows:

- sessile adenomas
- large broad-based pedunculate polyps
- early carcinoma (pT1) in good or with medium differentiation adenomas within the extraperitoneal portion of the rectum

– carcinoma (pT2) in elderly, high-risk patients
– benign rectal tumours (lipoma, leiomyoma)
– diagnosis and centesis of haemorrhages
– correction of rectal stenosis
– closure of fistulas
– rectopexy

TEM has been developed mostly for lesions out of reach from the transanal approach. It could be used also for large benign lesions above the peritoneal reflection.

Favourable T1 lesions have equivalent local recurrence rate and 5-year survival compared to radical surgery. Unfavourable T1 lesions have higher local recurrence (10–15%). TEM+radiation therapy on T2 tumours have local recurrence of 25–46%.

Most larger mid-rectal and high rectal polyps have recently been managed by means of gas-filled endorectal excision, using the TEM technique. Although this technique has many advocates in Europe, in the USA it has mostly been ignored [8]. But from time to time there are also reports from the USA describing first experiences with TEM [9]. They succeeded in providing excision of rectal lesions with negative margins in 97% of cases with minimal morbidity and short-duration hospital stay. Their follow up was too brief to evaluate recurrences, but the thoroughness of resection of the tumour in a high proportion of cases was promising.

Endoscopic microsurgery is at the moment the most advanced procedure in the field of intraluminal surgery [10]. At the same time, endoscopic microsurgery, which has been in the clinical routine since 1983 [11], was the first complex endoscopic operation to be routinely applied in gastrointestinal surgery. The procedure is performed using the operative rectoscope. A number of endoscopic instruments have been designed for TEM. CO_2 insufflation must be performed by use of various systems, dealing recently with TEM. Also very special combinations of instruments exist for the dissection. They allow optimal handling and electronically controlled switching between the bipolar and cutting mode and the monopolar coagulation mode. The most modern electrosurgical systems come from Germany. They are constructed to be multifunctional (ERBE TEM 400), uniting bipolar cutting, monopolar coagulation, suction and irrigation. There is no need to change instruments during the operation as there was several years ago. The cutting needle extends automatically when the cutting function is activated and retracts automatically at the end of cutting. This ensures safe cutting (Fig. 5). Synchronous and intermittent suction and irrigation facilitate the surgical procedure. Suction is always provided due to the roller pump.

Their advantages are:
– streamlined surgery via a multifunctional instrument with cutting, coagulation and suction/irrigation functions
– shorter procedural time
– shorter operations
– less morbidity (infection, incontinence)

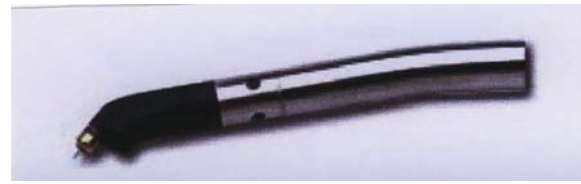

Fig. 5. Multifunctional instrument (ERBE TEM 400)

Other sophisticated improvements are described every year. One of them is dye-enhanced selective laser ablation [12], which uses a diode laser, operating at a wavelength of 805 nm. Indocyanine green (ICG) has a maximum energy absorption of a wavelength of approximately 800 nm. The effect of the diode laser as a laser knife can be significantly enhanced with an injection of ICG. The dye-enhanced photothermal effect was investigated by the Japanese. Their experiences with resection of 5 rectal tumours by means of TEM were very good due to precise haemostasis and its excellent tissue cutting effect.

As mentioned above, TEM involves the use of expensive equipment, which is not widely available, while posterior approach techniques have lost their popularity due to the high incidence of post-operative complications [13].

Positioning of the Patient

The patient is in such a position that the lesion should be on the bottom of the operating field. This is usually the prone lithotomy position, but also on the left or right side or in the jack knife position if the lesion is ventral. Rigid rectoscopy must be performed to determine the position of the patient on the operating table.

An intraluminal ultrasound examination should be performed pre-operatively in all patients. If there are suspicious lymph nodes, TEM is indicated only as a palliative procedure.

The Technique by Means of Salvati's Operating Proctoscope

The cheaper modality offers Salvati's proctoscope, originally designed for electrocoagulation for rectal cancer [14]. Salvati believed that electrocoagulation could be a primary therapy for early rectal cancer. Further experiences were published, e.g., Zammit et

al. [15]. Today it is a useful instrument for perianal resection of rectal tumours under direct vision. The main features are its wide lumen (4 cm in diameter), an oblique end, a smoke evacuation channel and a light channel. It is insulated to protect from diathermy damage and comes in 2 lengths: 12 and 19 cm.

This technique does not differ from TEM in the positioning of the patient, infiltration of mucosa and the use of various regimens of diathermy. It is important to resect the specimen in one piece as tumour fragmentation increases the risk of recurrence [16].

Recurrence Rate After Local Excision of Rectal Cancer

Increased incidence of local recurrence rate and decreased survival is the main problem of local resections (for cancers) when compared to radical surgery. The rate of local recurrence has been reported to occur in 0–37% of patients with T1 or T2 cancers [17, 18]. Table 3 shows the recurrence rates in recent series using various techniques. Although TEM seems to be associated with a lower local recurrence rate (9 vs. 22%), one must note the shorter follow up in the TEM patients and the more favourable pathology (71% Ca in situ/T1 in TEM vs. 57% in local resection). Also, the local resection articles tend to include patients that had other techniques such as Localio (Kraske), Mason or fulguration.

The increased risk of local recurrence following local resections is due to the less radical nature of surgery and the fact that perirectal nodes are not excised. Thus patient selection is based on selecting tumours with a low risk of lymph node metastases. Histological features associated with increased risk of lymph node metastases are: poor differentiation, lymphovascular invasion and more advanced T stage. If any of these histological features are found, then one should consider adjuvant therapy or performing radical resection [16, 19]. However, the risk of lymph node involvement is present in all cancers. Blumberg et al. [20] found that even T1 cancers (that underwent a radical resection) with no adverse histological features had a 7% risk of lymph node involvement.

Salvage surgery for recurrences is only successful in 45–60% of cases that were initially treated with local resection for Stage I rectal cancer [21].

A very interesting use of TEM has been described by Lev-Chelouche et al. [22]. He pointed out synchronous colorectal neoplasms that are a common pathology which at times necessitate extensive abdominal surgery. When one of the lesions is located in the rectum, the operation has even higher rates of morbidity and mortality. In such cases, they suggested a two-step procedure, comprising TEM resection for the rectal tumour followed by a less extensive abdominal resection for the second.

Technique of TEM

Pre-Operative Examination

Complete pre-operative coloscopy is mandatory. Information from flexible endoscopy concerning the height of rectosigmoid lesions is unreliable, therefore rigid rectoscopy is also recommended. During the rectoscopy, the lower and upper margin of the tumour and the precise position in the circumference are defined. This information is also important for the proper positioning of the patient on the operating table.

Endoluminal ultrasound is mandatory in all patients to ascertain the depth of penetration and thus the stage.

Pre-Operative Preparation

Informed consent is explained to the patient, including the risk of conversion to laparotomy in patients with proximal lesions. We use the standard orthograde mechanical bowel preparation. Short-term antibiotic prophylaxy is used too.

Operation

The operation is performed under general anaesthesia. The patient is placed in the dependent position, as described during the pre-operative examination. The most difficult position is the prone position. This position, for tumours of the anterior wall, requires strong support of the hips and chest so the abdomen itself is mobile. When the lateral Simms position is necessary, it is important that the anus is accessible and the table or legs of the patient do not impede mobility of the instruments. Suitable positioning of the patient is necessary because of the angulation of the optics and the specific design of the instruments.

A careful digital sphincter dilatation is performed. The operative rectoscope is introduced and the tumour is localised. The position of the rectoscope is fixed by a special retractor. The operative instruments and the optics are introduced and connected to the different lines.

The type of excision depends on the type and position of the tumour. The standard is the full-thickness excision because tearing of the tumour is prevented and precise histological evaluation is possible. In the case of a carcinoma inside an adenoma, full-thickness

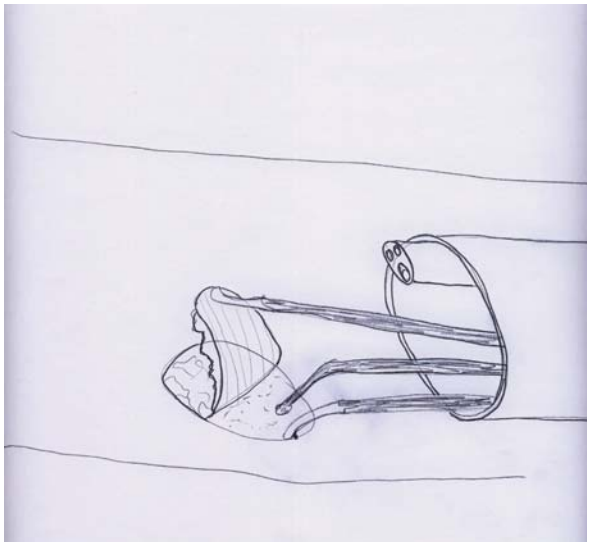

Fig. 6. TEM dissection technique

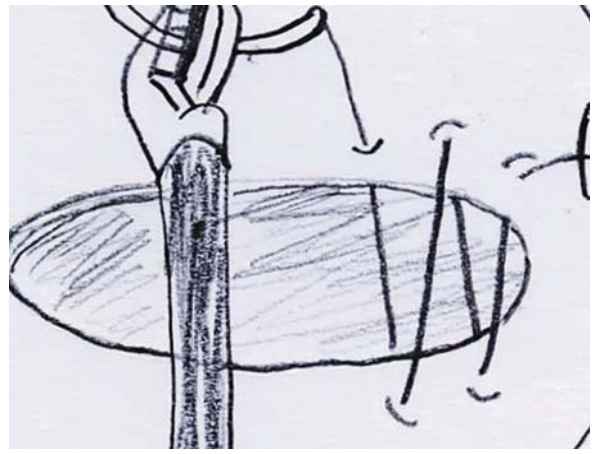

Fig. 7. TEM suturing technique

excision is mandatory to guarantee complete excision. Full-thickness excision of an anterior wall above 10 cm is not possible because of the contact to the peritoneal cavity. In women this limit could be even lower. The resection line for the dissection is defined by placing marking dots using a high frequency cautery device. The line should be 5 mm long for adenomas and at least 10 mm long for early cancers. After placement of the marking dots the bowel wall is transected to the appropriate layer by use of the standard technique. A monopolar cutting device is used. When bleeding occurs, the suction device, which is positioned at the entrance of the rectoscope, is advanced and the bleeding is localised and stopped by monopolar coagulation. Dissection from the perirectal tissue is usually performed in a layer close to the longitudinal muscles of the bowel wall and the tumour lifted upward (Fig. 6). Any bleeding must be stopped immediately by monopolar coagulation to guarantee optimal overview during the whole procedure.

Suturing

All defects are closed at the conclusion of the dissection. The defect is closed by transverse continuous suture, using monofilament thread. Before suturing, the area is rinsed thoroughly with beta-iodine. The suture starts at the right corner (Fig. 7). At the end of the suture a silver clip is placed onto the thread. The clip is a fast, safe and secure substitute for knotting. In semicircular defects and segmental resections, stay sutures first are placed so that the suture line is geometrically predefined and tension during suturing is reduced.

Post-Operative Treatment

Following mucosectomy, all patients are given oral nutrition on the first post-operative day. After full-thickness resection, parenteral nutrition is maintained for two days while allowing a clear fluid diet. In larger resections, this regimen is maintained for at least five post-operative days. It does not from differ the post-operative management after open surgery.

Results

The technique of TEM was introduced into clinical practice in Cologne, Germany, 1983. In the Czech Republic, the first intervention was performed in České Budějovice in 1992. Kyjov had the first TEM equipment in 1996, and Brno had it in the same year. Recently, in Czechia, there were 13 surgical departments with TEM equipment. Till 2003, 285 patients had been operated on in České Budějovice, 393 in Kyjov and 298 in Brno. So there are 976 patients in these 3 centres (Table 1). The others have smaller

Table 1. TEM 1992–2003

	∑	Polyps	Ca	Others
Č. Budějovice since 1992	285	193	65	15
Kyjov since 1996	393	209	160	24
Brno since 1996	298	158	122	18
∑	976	560	347	57

Table 2. Polypectomy methods

1992–2003	Surgical methods used
TEM	560
Transanal	60
Parasacral	36
Trans-sphincteric	24

experiences, so we have not included them in our statistics.

In the above-mentioned centres 560 patients were operated on because of benign polyps, 347 because of early cancer and 57 due to other diagnoses. In the same period, other surgical methods were used too (Table 2). Thirty percent of the adenoma group was treated by a mucosectomy, 66% by a full-thickness excision and 3% by segmental resection. The average operating time was 77 min for mucosectomy, 122 min for full-thickness resection and 184 min for segmental resection. The tumour size ranged from 0.8 to 65 cm^2. The average was 16 cm^2.

Complications occurred in 6.6% of the polyp group. Two patients required colostomy caused by dehiscence of the suture line, 1 developed rectovaginal fistula, seven had post-operative bleeding and required transanal haemostasis.

In the carcinoma group, 11% required surgical intervention because of complications. Five underwent Hartmann's procedure and colostomy caused by suture line dehiscence. Thirteen patients underwent low anterior reresection due to carcinoma recurrence. Eight underwent abdominoperineal resection. In only three was radiotherapy applied.

As to other indications, there was inflammatory bowel disease in 19, fistulas in 15, stenoses in 10, endometriosis in 6, foreign body in 3 and bleeding in 4 patients. The conversion rate was 4% (perforation, bleeding and too large tumour).

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Low Anterior Resection

Adam Dziki

Introduction

Low anterior resection (LAR) is a surgical technique applied for the resection of malignant and benign tumors located in the middle and low part of the rectum. The principals include of the technique mobilising the rectum, performing an anastomosis below the anterior peritoneal reflection and mobilising the splenic flexure.

Bowel Preparation

Infectious complications of colorectal surgery include wound infection, intra-abdominal or pelvic abscesses, and anastomotic leak. They are mainly caused by endogenous colonic cultures. It seems logical that reducing faecal load and the bacterial count in the intestinal lumen should reduce the rate of infections. Bowel preparation before surgery of the colon and rectum consists of mechanical bowel cleaning from residual stool mass and administration of pre-operative intravenous antibiotics. The essential aims are: comfort, assurance and clean environment in the operative field during surgery, reduction of intestinal flora and decrease in the rate of post-operative infectious events. When the colon is evacuated of stool mass, the amount of bacteria is decreased and mechanical disruption of the anastomosis by shaped, dense passing stool is possibly prevented. Each of the surgical centres usually uses their own methods of effective bowel preparation that have been tested over many years.

Mechanical bowel preparation is performed either by oral ingestion of cathartic agents or by enema irrigations. Historically, castor oil, anthroquinolones such as senna, diphenylmethanes such as bisacodyl, and salts such as sodium picosulphate and magnesium citrate in combination with a low residue diet and mannitol as an osmotic agent were used. At present, polyethylene glycol and sodium phosphate are most common. Polyethylene glycol provides a good quality of bowel cleansing from stool mass [1, 2]; it is popular and has well proven efficacy [3–5]. Intolerance resulting from a necessarily large volume of oral water intake (4 l) may appear occasionally in a group of patients. The symptoms include nausea, discomfort, vomiting, abdominal pain and distension [6, 7]. Sodium phosphate is equally effective with the benefit of no adverse events [7, 8], but causes a huge electrolyte imbalance, sodium phosphate should not be used in patients with chronic renal failure, cirrhosis of the liver, advanced heart failure and in patients with symptoms of ascites [9]. Patients tolerate sodium phosphate better but polyethylene glycol was proved to be safer.

During recent years a few studies have shown that colorectal surgery with no mechanical bowel preparation is equally safe and is not associated with higher rates of post-operative adverse events (wound infection, intra-abdominal abscesses, anastomotic leak) [10–13].

The Author uses mechanical bowel preparation with polyethylene glycol before each rectal resection. Despite many studies proving no benefits of bowel preparation, mechanical cleaning of the bowel makes the operation more comfortable for the surgeon, particularly during anastomosis formation. In connection with some unfavourable aspects resulting from mechanical bowel preparation, many surgeons asked if there is a need for pre-operative preparation.

In the past, bowel preparation consisted of administration of non-absorbable antibiotics to reduce the growth of endogenous colonic bacterial culture. For some years information referring to the efficacy of pre-operative bowel preparation has been inconsistent. Some studies demonstrated benefits of a pre-operative neomycin and erythromycin administered in combination, whereas several papers found them to have no effect [14-17]. Nowadays the application of those antibiotics has been given up.

Prophylactic use of pre-operative intravenous antibiotics is a standard procedure in all colorectal surgery. The efficacy of antibiotic infusion (most often second generation of cephalosporins and metronidazole) pre-operatively is well documented

[18]. Unfavourable aspects of prophylactic use of antibiotics are the high costs of the application, the selection of severe and resistant bacterial cultures and also the risk of toxic colitis in the course of a Clostridium difficile infection [19].

Surgical Technique of the TME

Total mesorectal excision (TME) is a relatively new modification of the standard procedure of LAR. The technique was first described by Heald and Ryall [20] and became a widely accepted surgical standard in the treatment of cancer of the rectum. The principle of the procedure involves complete removal of the mesorectum and the mesentery containing the inferior mesenteric artery and vein. The method combines what seems impossible: oncological radicality and preservation of pelvic autonomic nerves. The key step of the procedure is the identification and consequent preservation of the pre-aortic superior hypogastric plexus as well as laterally located hypogastric nerves and sacral splanchnic nerves forming inferior hypogastric plexus on both sides of the pelvic wall.

The introduction of TME together with a high ligation of the inferior mesenteric artery and adequate distal margins of safety has led to a significant reduction in local recurrence rates as well as a reduction in bladder and sexual function impairment [21].

Operative Procedure

Surgery begins with the mobilisation of the left colon and sigmoid. The peritoneum over the lateral part of the descending colon and sigmoid colon has to be divided along the line of attachment of the peritoneum to the sigmoid colon mesentery. It can be best achieved by using electrocautery or sharp dissection with scissors. Careful preparation allows us to enter the avascular, alveolar space of the left iliac area with its structures: left urethra crossing iliac common artery and vein as well as iliopsoas muscle. At this point the descending colon and sigmoid can be gently mobilised and colonic vessels separated from the urethra. Identification of the left urethra is one of the crucial points of the operation because it can be easily injured while the operation advances. The incision of the peritoneum has to be extended downward to reach the posterolateral aspect of the left side of the pelvis. On the right side the division of the peritoneum has to be carried out over aorta and right posterolateral aspect of the pelvis. This incision should expose the origin of the inferior mesenteric artery and vein. The dissection and ligation of the mesenteric vein should be done first to prevent the spread of tumour cells into the bloodstream during manipulation of the rectum. The level of the dissection of the mesenteric artery is very important. The sympathetic trunks along the aorta send sympathetic nerves medially to the anterior surface of the abdominal aorta and form inferior mesenteric plexus at the level of inferior mesenteric artery. In order to prevent nerve damage, high ligation of the inferior mesenteric artery has to be done. The transection line should be roughly 1–2 cm distant from the aorta. This level represents also the cranial boundary of the mesentery lymph node package; lymph node metastases are rarely found at the point of origin of artery.

After dissection of the mesentery vessels, pelvic dissection commences. The dissection should begin laterally and to the right of the promontory; at this point the identification of the avascular “holy plane” is best performed. Identification of the holy plane is a prerequisite for the surgical procedure. It should be done under direct vision and tearing of the mesorectum should be avoided. Below the aortic bifurcation, presacral sympathetic nerves form the superior hypogastric plexus, which is approximately at the level of the promontory. The plexus is covered with a thin layer of connective tissue and fat. The plexus then divides to form hypogastric nerves. The right and left hypogastric nerves run within the space between visceral pelvic fascia of the mesorectum and parietal pelvic fascia of the pelvic wall. The dissection has to proceed in the posterior plane between those two fascias. When the plane is identified correctly, the dissection goes through an avascular areolar space. It can be performed with the help of a water-jet device, electrocautery or sharp scissors. Blunt finger preparation should be avoided. Dissection in the posterior plane usually does not create any problem and can easily be continued till the tip of the coccyx (till the pelvic floor). Posterior dissection should be extended laterally. Dorsolateral dissection usually mobilises the rectum sufficiently to pull it out of the pelvis to some extent but it remains fixed to the pelvic wall on both sides laterally. Standard technique of LAR involves ligation of the lateral ligaments of the rectum; these structures are however small nerve branches and minor vessels arising from the branches of the internal iliac artery, which pass to the mesorectum through inferior hypogastric plexus. Preparation in the right plane and proper use of diathermy should eliminate bleeding from those structures. The “lateral ligaments” should not be clamped and ligated. When the lateral and posterior dissections are complete, the attempt should be made to start the anterior part. This is the most difficult part of the surgical procedure. Anterior rectal wall, posterior wall of the bladder, the prostate and semi-

nal vesicles or the posterior wall of the vagina originate from the same embryonic tissue, therefore there is no clear plane separating these structures. The peritoneum over the retrouterine or rectovesical pouch should be divided. In the male the anterior wall of the rectum is covered with the 0.5–1-cm layer of mesorectum, therefore incision of the peritoneal reflection should be done over the bladder in order to avoid entering the mesorectum. Great care has to be taken laterally dissecting the Denonvillier's fascia where the inferior hypogastric plexus gives rise to the neurovascular bundle of Walsh which runs along the posterolateral aspect of the prostate. In the female the mesorectum is often very thin and therefore in direct contact with the posterior wall of the vagina. The crucial part of this part of the procedure is careful separation of the structures preferably with diathermy or water-jet in the plane between the Denonvillier's fascia and seminal vesicles in male and posterior wall of the vagina in females. The dissection behind the fascia should be natural continuation of the lateral dissection.

Following complete mobilisation of the rectum including mesorectum-free distal part of the intestine, the linear stapler is used to divide the rectum. Some Authors advocate the double-stapling technique.

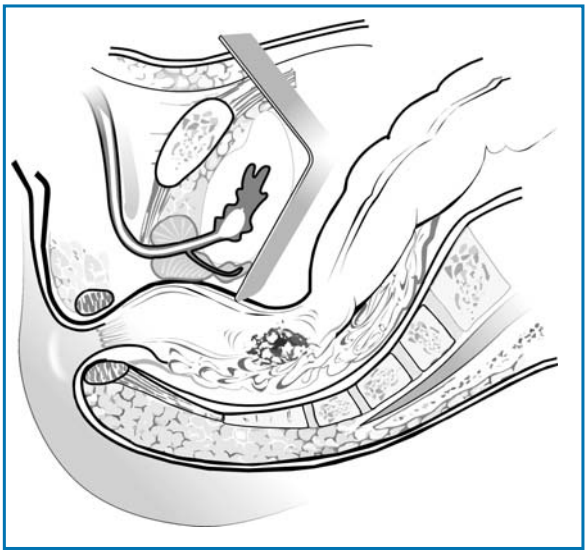

Fig. 1. Location of the local tumour in the relation to the mesorectum

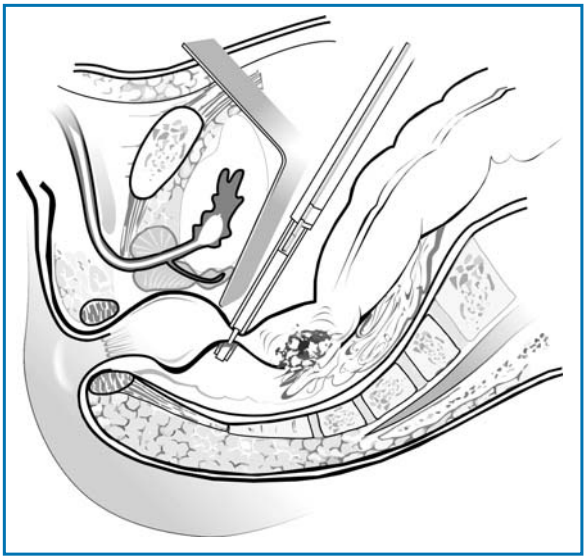

Fig. 2. Closing the rectum with the linear stapler

Damage to the Pelvic Autonomic Nerves

Damage to hypogastric and splanchnic sacral nerves during conventional operations for rectal cancer result in very high rates of sexual dysfunction comprising up to 85% of surgery patients [22, 23]. Bladder dysfunction as reported by different Authors varied between 7 and 73% [24, 25]. What is equally important from the oncological radicality point of view are very low local recurrence rates, which are the result of an adequate removal of the tumour using the TME technique and have been reported by several Authors [26, 27].

Performing LAR, an end-to-end anastomosis between descending colon and rectum stump has to be performed. The distal margin should be a minimum of 2 cm; in low-grade tumours this distance can be smaller. A circular stapling device is used to create the anastomosis. Single- or double-stapling technique can be used. In the case of single stapler use, transection of the bowel is performed with a cutter. Purse-string clamps are placed on both proximal and distal stumps (Fig. 1). The anvil is inserted into a proximal stump. The circular stapler (without its anvil) is inserted transanally. After exteriorising the trocar, the purse-string is closed around its base. The last steps of the procedure include closing, firing and removing the stapler (Figs. 2, 3). But the most popular technique used worldwide is the double-stapled technique. This entails transection of the rectum distal to the tumour from within the abdomen using a linear stapling device (Fig. 4). The proximal resection margin is divided with a purse-string device. After sizing the lumen, the detached anvil of the circular stapler is inserted into the proximal margin and secured with the purse-string suture. The circular stapler is inserted carefully into the rectum, and the trocar is projected through or near the linear staple line. This is quite an important moment – the trocar

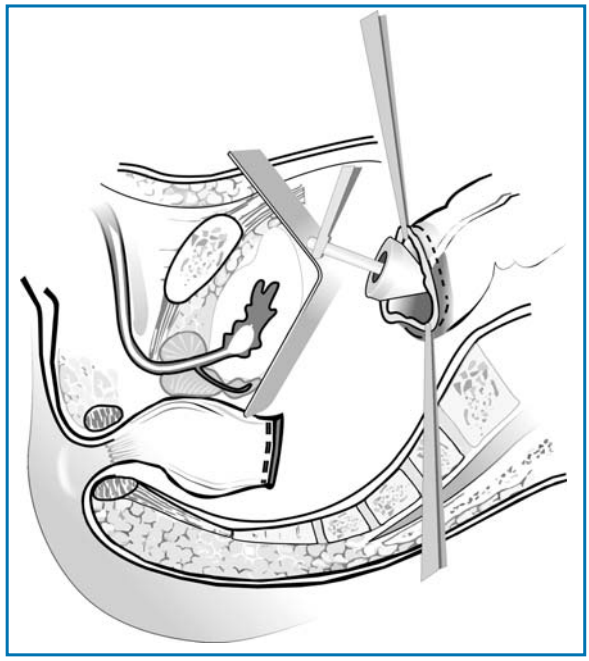

Fig. 3. The anvil is placed into the proximal stump

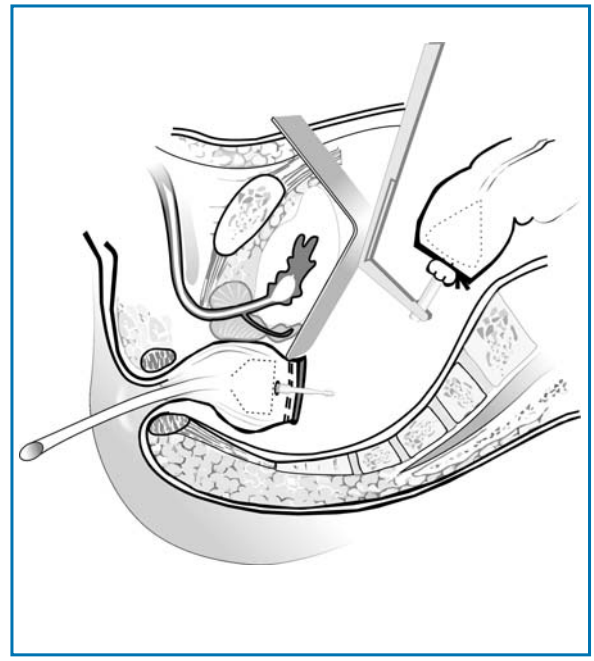

Fig. 4. The circular stapler is inserted transanally

should pierce the anterior wall as close to the staple line as possible (Fig. 5). Then, the anvil is engaged with the trocar and, after completely closing the circular stapler, the device is fired. Two rings of staples create the anastomosis, and a circular rim or donut of tissue from the proximal and distal margins is removed with the stapling device (Fig. 6). The anastomotic leakage rate with this technique ranges from 3 to 11% for middle-third and upper-third anastomoses and to 20% for lower-third anastomoses. For this reason, some surgeons choose to protect the lower-third anastomosis by creating a temporary diverting stoma. This is especially important when patients have undergone a pre-operative RT course. A handsewn anastomosis may be performed; if preferred, the anastomosis is performed as a single-layer technique. Usually the handsewn technique is limited with the location of the tumor – if we really mean LAR, this procedure is usually possible only with stapling techniques. The leak and stenosis rates are the same for stapled and handsewn anastomoses.

Very low rectal cancers, located just above the sphincter occasionally can be resected without the need for a permanent colostomy. The procedure is as already described; however, the pelvic dissection is carried down to the level of the levator ani muscles from within the abdomen. A straight-tube colo-anal anastomosis (CAA) can be performed using the double-stapled technique, or a handsewn anastomosis can be performed transanally. This last option is also

Fig. 5. Exteriorised trocar seen from the rectal stump

a rescue technique when we need to take down stapled CAA, due to some major leak during anastomosis testing. Some surgeons do not want to perform stapled CAA because of the possibility of implantation of malignant cells at the stapled transection line. The first stage of the procedure is to deliver descend-

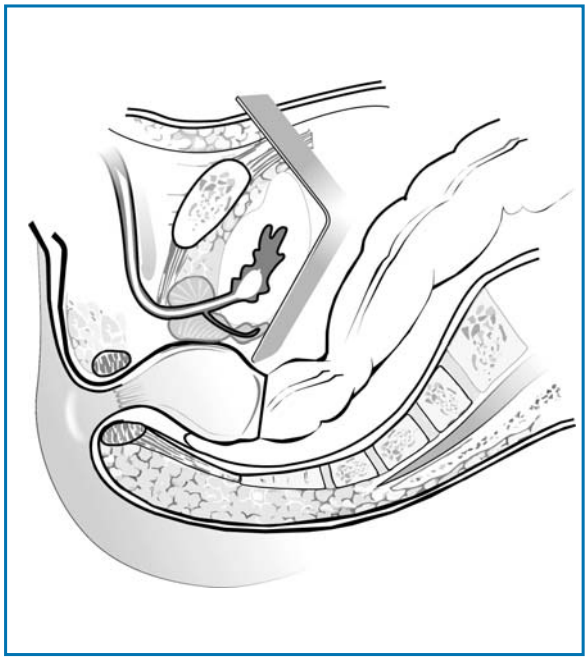

Fig. 6. Anastomosis done with the stapling technique

ing colon to dentate line without tension. After that, the end of the colon and anal canal mucosa with internal sphincter are sutured using single, full thickness sutures.

The best way to test the anastomosis after LAR is to place a 30 FR catheter through the anal sphincter and fill the pelvis with 0.9% saline. Then with a 250-ml syringe, insufflate the rectum with air; the bowel above the anastomosis is held by a noncrushing clamp. If anal anastomosis is checked, it is enough to place the syringe nozzle within the anastomotic area. In case of any doubt about anastomosis consistence, one or two sutures should be added into the site of the suspected leak, and after that the anastomosis should be rechecked. If there is still no evidence of complete anastomosis integrity, a proximal protective stoma should be performed.

Colonic Reservoirs

LARs due to cancer of the mid and low rectum can lead to functional impairments of sexual, urinary and continence dysfunctions. Low or very low end-to-end anastomosis using either stapled or handsewn technique enables gases and stool to collect, resulting in urgency and problems with continence, especially during the first year after surgery. Colonic reservoirs as options of "neorectum" are created to improve bowel function in patients undergoing LAR with CAA. "J-shaped" colonic and transverse coloplasty pouches are the available ways of restoring the neorectal reservoir [28].

J-Shaped Colonic Pouch

In 1986 a colonic J-pouch was described by Parc et al. [29] and by Lazorthes et al. [30], independently, to replace the excised rectal reservoir. The procedure comprises of identification of limbs with closed distal colon and seromuscular apposition. Long colotomy, closure of posterior and anterior wall may be performed using either conventional continuous suturing or a GIA stapling device with the final attachment colonic pouch to the anus with circular stapler. Ideal pouch dimensions are 6–7 cm of bowel circumference and with limb lengths about 5 cm. Most surgeons are of the crucial step of the procedure is mobilization of the splenic flexure of the colon and preserving the first branch of the inferior mesenteric artery to enable blood perfusion through the pouch [28]. Patients with colonic J-pouch may experience varying degrees of incomplete defecation requiring provoked evacuation with laxatives or daily enema use, unless J-pouch limbs are limited to a 5 cm size [31].

Inability to perform colonic J-pouch arises from some technical reasons, and therefore in about 25% of patients are unable to have a colonic J-pouch. Difficulties in creating a colonic J-pouch include:

- narrow pelvis (especially male patients)
- bulky colonic pouch
- long anal canal with prominent sphincters
- short fatty mesocolon
- diverticulosis
- insufficient colon length.

Benefits of colonic J-pouch are better rectal compliance and higher maximal tolerable rectal volume which can lead to improved rectal function after LAR [32, 33].

Transverse Coloplasty

A transverse coloplasty was first described (by Z'graggen) in 1999 and facilitate the construction of a pouch anal anastomosis. The pouch is performed by making an 8–10-cm longitudinal colotomy, 4–6 cm from the distal cut end of the colon. The colotomy is made on the antimesenteric side of the colon between the taenia. Colon is then sutured transversely with 3-0 polyglycolic acid seromuscular threads similarly to the Hainecken-Mikulicz plasty. Finally end-to-end stapled anastomosis is performed with CAA stapler [34].

Transverse coloplasty requires less space in the pelvic area than colonic J-pouch, therefore it is technically more suitable, especially in the narrow male pelvis. Short- and long-term follow-up show similar functional results of these two types of rectal pouches [35].

Side-to-End Anastomosis

The method of side-to-end anastomosis of the colon and rectum has been advocated to deal with the disparity between the two lumen. To create the modality the double-stapling approach can be used. Rectal stump is closed with a linear stapler. A proximal anvil is inserted in open sigmoid or descending colon and passed through the antimesenteric colonic wall. The end of distal colon is closed and the stapling completed in the usual manner [28, 36].

Rectal reservoirs should be considered, especially for anastomosis at or below 4 cm from anal verge. Traditionally a colonic J-pouch may be constructed if technically possible. Coloplasty seems to be an attractive modality to colonic J-pouch. Complications associated with the anastomosis do not differ in both groups, however colonic J-pouch patients with handsewn anastomosis had a higher anastomotic leakage rate than the patients in the coloplasty with handsewn anastomosis group [35].

Transverse coloplasty functional results are similar to those after colonic J-pouch construction and outcomes of both reservoirs are superior to straight end-to-end anastomosis [33, 35]. Colonic J-pouch and side-to-end anastomosis give comparable functional results two years after LAR [37].

However, long-term results show that there are no functional differences between described modalities and after a two-year post-operative follow-up study, quality of life outcomes also become similar. Thus, after this period, the presence of colonic reservoirs actually does not influence bowel habits or problems associated with so-called “low resection syndrome”, especially after straight anastomosis. They should be considered to diminish the functional impairment in the early post-operative period after very low rectal cancer.

Lateral Lymphadenectomy

Spread of rectal cancer via lymphatic vessels results in the involvement of lymph nodes, located both upward and lateral. Lymphatic vessels go from the lower rectum through the lateral ligament and reach iliac lymph nodes, so that lateral ligament is believed to be crucial in the lateral lymphatic flow [38]. Lateral lymphadenectomy is mainly practised in Japan. Lateral lymph nodes (middle rectal, obturator, internal iliac lymph nodes) are metastatic when tumours are located at or below the peritoneal reflection. The percentage of lateral lymph node involvement is assessed by many Authors on average as 9–18% and it ranges from 2.8% for T1 to 31–40% for T4 rectal tumours [39, 40]. All the Authors confirm that the percentage of lateral lymph metastases strictly depends on tumour growth. It was also observed that for the tumors with a lower margin above 6 cm from the dentate line, metastases in lateral lymph nodes occurred only in 0.6% of cases, while in tumours with lower margin below 5 cm above this line it ranged from 7.5% (for tumors between 4.1 and 5 cm) to 29.6% (for tumors between 0.1 and 1 cm). The main reason pelvic lymphadenectomy in rectal cancer (complete clearance of lateral lymphatic nodes) is performed is to improve survival and reduce local recurrence. However, retrospective studies conducted by many Authors confirmed no improvement in a 5-year survival rate in the patients in whom this procedure was performed when compared to the groups where conventional operations were conducted [39, 41, 42]. Moreover, it is highlighted that the risk of urinary and sexual dysfunction linked with lateral lymphadenectomy is too high and outweighs the risk of local recurrence associated with the presence of potential metastases in lateral lymph nodes [42]. It is still unclear whether extended pelvic lymphadenectomy is an appropriate approach and it is very important to establish precise indications for carrying out this procedure.

Protective Stoma

Temporary loop ileostomy or colostomy after LAR is usually considered in order to protect either colo-anal or colorectal anastomosis.

Relative indications for creating protective stoma are:

- very low anastomosis (colo-anal)
- pelvic sepsis
- blood loss leading to chronic anaemia
- poor nutritional status
- obstruction
- perforation of the tumour
- pre-operative chemoradiotherapy
- other systemic diseases [28].

If there is any concern about the integrity of anastomosis, diverting stoma should be made, especially in the case of tension on the suture line.

If the patient has received pre-operative chemoradiotherapy, temporary ileo- or colostomy should be made to enable complete healing of the anastomosis [43].

It is generally believed that now when the stapled technique has been introduced and handsewn anastomosis performed less and less, diverting stoma is avoided more often. It is also believed but not well proven that mechanical suture offers greater confidence of anastomosis than a manual procedure.

Loop ileostomy seems to be easier to perform than transverse protective colostomy. Some Authors find colostomy associated with a higher risk of complications in contrast with others, suggesting that creating and closure of loop diverting ileostomy is safer [44, 45].

The morbidity of ileostomy and colostomy closure, unless decreased, remains an important issue [46]. Some Authors suggest closing the protective stoma during the same hospitalisation, 7 days after the resection. In my opinion, early closure is associated with higher risk of complications even including post-operative mortality. The interval between creation and closure of the stoma should be at least 6–8 weeks. Longer periods between these procedures correspond with better outcomes. Simple closure of the colostomy is safer than resection of the colon in order to close the stoma [43].

During closing of the colostomy, special emphasis should be put on the integrity of marginal artery as it can be the only vessel that supplies blood to the distal colon down to the anastomosis. The consequences of ligation of the vessel are obvious and result in necrosis of the distal colon after anterior resection of the rectum.

One of the most common complications of closure of the stoma (especially colostomy) is wound infection, however it may be avoided by delayed wound closure but with primary packing of gauze with antiseptic solution. The secondary closure of the wound can be performed 3–4 days after the main closing procedure [28, 43].

The type of a protective stoma should be considered and individualised to the patient's conditions. Both types of stoma carry a high complication rate with a considerable mortality rate. The interval between stoma construction and closure has substantial impact on social and economic status [47]. Closure of the stoma is not free from complications, including post-operative mortality, thus the decision of closing should be also made after careful consideration [44, 46].

Drainage After LAR

The principle of post-operative surgical drainage is to perform it when one expects a risk of fluid collection. In the case of LAR of the rectum, there are three potential benefits of drainage. First, it can be helpful in recognition of post-operative bleeding; second, it helps to detect anastomosis leakage; and third, it protects against fluid collecting in potentially contaminated region of anastomosis, thus preventing abscess formation [48]. However, drainage after anastomosis below the peritoneal reflection remains controversial and according to the literature, in most of these cases drainage is not performed.

There are very few randomised trials comparing prophylactic pelvic drainage *vs.* no drainage after LAR [49–51]. In all studies outcomes were measured by percentage of mortality and presence of clinical anastomotic leakage, as well as by radiological anastomotic dehiscence, wound infection, re-operation and extra abdominal complications. Statistically significant differences between measured items in the two groups of patients were not observed in any of these studies.

Similarly, the studies underscore the low sensitivity of drainage in detecting leakage and post-operative bleeding, questioning its supposed warning function. So far there is not sufficient evidence confirming that prophylactic drainage in elective LAR reduces rates of complications and prevents anastomosis.

Another controversial aspect is duration of the drainage. It ranges from 3 to 7 days. Some authors indicate the need for further trials on drainage duration, especially focusing on comparison of short-term drainage with no drainage and longer drainage [52, 53]. This has not yet been investigated.

In our department we routinely use two Redon drainages when low interior resection of rectum is performed. In most cases they are removed on the second day after the operation as we noticed that at this timepoint drains stop collecting fluid. In my opinion drains prevent fluid (blood) collection and abscess development in the area of anastomosis. In view of the literature data it is necessary to perform further investigations to confirm the prophylactic role (or its absence) of drainage after LAR.

Radiotherapy

Talking about colorectal cancer we must remember that although pathologically we consider adenocarcinoma of the colon and adenocarcinoma of the rectum as one disease, these two entities differ from each aspect: Anatomical differences in vascularisation, lymphatic drainage and absence of a visceral layer beneath perineal reflection result in different risks of local recurrence after curative intent surgery. In 1974, the problem of local recurrence after low resection of the rectum was described by Gunderson. It was observed that tumours located beneath 12 cm

from anal verge have a direct route of spreading in the pelvis via vessels, lymphatic system and directly via contact with surrounding tissues. With the introduction of TME, the rate of local failure dropped radically [54]. Still, local recurrence is a major problem in rectal tumor surgery. Neoadjuvant and adjuvant radiotherapy (RT) were introduced to decrease the rate of local failure.

Neoadjuvant Radiotherapy

There are many reasons for advocating pre-operative RT of advanced rectal cancers:

- reduction of local recurrence rate (better local control),
- reduction of tumour cells' spread via pelvis in the course of surgery,
- reduction of cases of residual disease (microscopic disease),
- reduction of tumour stage (increasing the chance for sphincter-preserving surgery),
- reduction of tumour size and infiltration,
- lower morbidity in comparison to post-operative RT (especially connected with small bowel).

Other biological conditions supporting the role of pre-operative RT include higher level of oxygenising of tissues and sensitivity of tumour tissues to irradiation (no effect of ischaemic bed). The specific anatomical shape of mesorectum in pelvis results in a small circumferential margin when LAR is performed, which results in concerns about oncological clearance. Pre-operative RT improves this situation. The number of local recurrences is statistically lower with the use of pre-operative RT. In some cases the LAR is virtually possible because of RT.

In 1997, a Swedish trial showed a positive influence of pre-operative RT on life expectancy [55]. Unfortunately, no other trials have confirmed this conclusion. On the other hand there is a revolutionary paper describing 71 (28%) out of 260 patients with complete clinical response to pre-operative chemoradiotherapy who were not treated surgically [56].

It must be emphasised that precise estimation of tumor stage is the key to qualification for pre-operative RT. If the tumor is described as T1 or T2, surgery alone is standard. T3 tumors, short course pre-operative RT is advocated. Short course of RT comprises of total dose of 25 Gy, 5 Gy per fraction for 5 days and is given before consecutive surgery which follows 1 week after radiation. In case of T4 tumors, long course pre-operative RT should be introduced. The patient is irradiated 5 days/week for 5 weeks to the total dose of 45–50.4 Gy with 1.8 Gy per single fraction. It is mainly combined with 5-FU chemotherapy with (first and last week of irradiation). The surgery is performed 4–7 weeks after irradiation.

In the Uppsala trial in Sweden, adjuvant and neoadjuvant therapy were compared directly. The study revealed a significantly lower rate of local recurrence after the neoadjuvant mode of irradiation (12 vs. 21%) [57].

Although some authors suggest that in selected cases a sphincter-preserving operation could be performed because of the downstaging result of long course pre-operative RT [58], there is general agreement that the operation policy should not be changed after neoadjuvant therapy.

Beside the fact that more and more data are being gathered in favour of the pre-operative mode of irradiation, post-operative radiochemotherapy is still acceptable. It should be performed if post-operative pathological assessment reveals symptoms of cancer advancement. It is conducted in the following manner: radiation to the total dose of 45–50.4 Gy with 1.8 Gy per single fraction. The patient is irradiated 5 days/week for 5 weeks. It is combined with chemotherapy with 5 FU (6 courses, one week each; first and last week of radiation is combined with 3rd and 4th course of chemotherapy).

Talking about RT, we must remember about morbidity. Colitis, cystitis, wound healing problems and small bowel obstruction are the most frequent side effects of radiation. As LAR is performed more and more frequently, LAR syndrome is one of the most frequent side effects of RT is which is worsened by RT (15% LAR alone *vs.* 30% LAR plus RT) [59, 60]. The goal is that both neoadjuvant courses seem to result in less frequent complications than post-operative RT [59, 61]. This provides another argument in favour of pre-operative RT.

Results of the Treatment

One of characteristics of rectal cancer is a predisposition to local recurrence and distant metastases. Evaluation and comparison of the results of treatment presented by various centres are not easy because of differences in number of patients, interpretation of various statistical methods, and in the first place – lack of standard criteria for qualification of the patients. Numerous prognostic factors affect survival rate: stage of the disease, tumour localisation, complications (bowel obstruction, tumour perforation, haemorrhage), tumour morphology, histological findings, mucous secretion and (recently brought into discussions more and more often) quality of treatment connected with the surgeon's experience.

A modern surgical treatment of rectal cancer that leads to an improvement in results was introduced by

Dixon in the Mayo Clinic. In 1940 he performed partial anterior resection of rectum. A further improvement in the results of treatment was observed in 1977, when Turnbull introduced the "no-touch" isolation technique, which was the basis for the oncological aseptic technique during the operating procedure [62, 63]. The real revolution in surgical treatment was the introduction of the TME technique presented in 1980 by Heald et al. [64].

Studies comparing results of treatment utilising TME with the conventional technique clearly show benefits of the TME technique. Local recurrence rate in curative resection, during a 3–5-year period with TME is 3–11% [65–72] compared to 23–30% with the conventional technique [66, 68, 69]. Five-year survival rates after TME are 68–80%, and after conventional operations only 45% [73, 74]. Metastasis appearance is 23–25% after TME and 60–65% after conventional treatment. The above facts show the clear-cut position of TME as the golden standard in the treatment of rectal cancer. The next factor improving results of treatment of colorectal cancer is pre-operative RT, which is discussed separately.

We must remember that results presented are only average numbers, not taking into consideration various prognostic factors, which can influence results of the treatment of the rectal cancer. Basically, the most important and undisputed prognostic factor is the tumour stage, precisely described by the TNM system. Five-year survival rates in an analysed group of 15 000 patients were: stage I, 70%; II, 55%; III, 46%; and IV, 9% [75, 76]. Lymph node metastases as well as local cancer invasion in blood and lymphatic vessels cause further worsening of five-year survival. Positive resection margin always leads to the recurrence of the cancer.

Worse results of the treatment are usually described in younger patients, below 40 years of age [77–79]. An important fact is that in younger patients we are dealing with poorly differentiated and mucous secretion tumours more often. Other facts are the more aggressive and fast course of the disease and – unfortunately – late diagnosis, with large tumour and advanced stage of disease.

The influence of sex on survival remains uncertain. A statistically significant worsening of 5-year survival rate in men compared to women was observed in many studies [79-81]. But worse prognosis for men was observed mainly in Dukes B and C stages. Numerous recent studies do not show a significant influence of sex on survival rate or recurrence of the disease [82, 83].

Complications of rectal cancer, like bowel obstruction, haemorrhage or perforation, that usually are indications for immediate surgical treatment, correlate with crucial deterioration in treatment results. The complete 5-year survival rate is significantly lower, and cancer recurrences are more frequent than in uncomplicated cases. A worsening of the prognosis is connected with a low percentage of operative tumours, due to the advanced stage of the disease, as well as with the possibility of intraperitoneal spread of cancer cells, which have a capacity for implantation and growth [84, 85]. Another factor that affects results of treatment is an unintended tumour perforation during the scheduled operation of an uncomplicated tumour [86].

Histological grading of tumour has unquestionable influence on treatment results. Poorly differentiated tumours are characterised by aggressive and dynamic growth. This is connected with a significant decrease in survival rates [87], increased rate of total cancer recurrences [88] and local recurrences as well [78].

Tumour morphology is another factor that may affect recurrence prognosis. Raised tumours cause local recurrence less often then ulcerative tumours, coring into bowel wall [79]. The reason for this situation may be significantly lower cancer infiltration outside the bowel wall and lower rate of lymph node infiltration and distal metastases, in cases of rising type of growth tumours. Circular type of tumour growth is also connected with worsening of the prognosis [89]. Bad results are also proven in cases of mucous-secreting tumours [80], which appear in younger patients (less than 40 years) more often.

Recent studies show unquestionable influence of treatment quality and surgeon's experience on the results of treatment. Low-volume hospitals have significantly lower survival rates compared to high-volume centres. Surgeons well experienced in pelvic surgical procedures, as well as in bowel resections, have better results, lower recurrence rates and better long-term survival rates [78, 90].

Early and Late Complications After LAR

Anastomotic leakage has always been a major clinical problem in rectal or anal anastomosis, however this complication after LAR still remains a challenging clinical problem that can lead to significant morbidity and mortality. The use of stapling devices, performing mid and low rectal cancer resections with TME that require radical dissection may lead to a higher rate of anastomotic leakage. The reported clinical leakage rate after anterior resection varies from 3 to 21% depending on the level of anastomosis, the method of reconstruction and surgical expertise. The post-operative mortality associated with anastomotic complications ranges from 2 to 25%. On the other hand, the low local recurrence rate and

improved survival after TME supports the necessity of the removal of the entire mesorectum. A low level of anastomosis is usually regarded as the significant risk factor increasing anastomotic leakage rate. As reported by Vignali et al. out of 1014 stapled rectal anastomoses, the leakage rates were 7.7 and 1% from anastomoses at a level below and above 7 cm from anal verge, respectively. In the report by Law et al., age, level of the tumour, level of the anastomosis, concomitant resection of the other organs, stage of disease and the technique of anastomosis were not significant factors. They found the gender of the patients and the presence of a stoma were the most important and independent risk factors for anastomotic leakage. The difference may be explained by the anatomical differences of the pelvis between males and females and might only become significant when the anastomosis is performed at a low level. Leakage rate in men was 13.4% while that in women was 5.2% (p=0.049). The presence of a stoma was associated with a lower leakage rate. In the group with proximal diversion, the leakage rate was 4.8% while that of the group without diversion was 16.1% (p=0.008). Moreover, in the male patients, the leakage rates in those with and without proximal diversion were 5 and 27% respectively (p=0.001) and in the female patients the presence of a stoma had no effect of the anastomotic leakage rate. Therefore Law et al. recommend routine creation of a stoma in male patients.

However, the relationship between a diversion stoma and anastomosic leakage is more controversial. Many studies did not find a lower leakage rate in patients with proximal diversion. In patients with anastomotic leakage, both conservative and surgical options (diversion stoma, Hartmann's procedure) may be considered. Conservative treatment for anastomotic leakage is usually possible in the presence of proximal diversion. Although the double stapling technique enables low rectal anastomoses, the transanal CAA still has its role. According to some surgeons, tumours at a level 2–3 cm from the dentate line were treated with transanal CA to preserve the anal sphincter. Enker et al. reported the low leakage rate in CAA after LAR in 1985. Law et al. did not find any statistical difference in leakage rate between double stapling and handsewn CAA. The low leakage rate of CAA may be due to the routine proximal diversion in the CAA. The anal canal may have a relatively better blood supply as compared with the ischaemic rectum stump after TME. The routine use of J-colon pouch may also be one of the reasons accounting for the low leakage rate. Hallbook et al. reported significantly lower leakage rates in colonic J-pouch anastomosis than straight anastomosis in a multicenter prospective randomised trial [91-93].

Stapled anastomosis besides its advantages is associated with the higher rate of anastomotic stenosis or stricture. The exact incidence of this complication is difficult to determine because the definition of stenosis is not well defined. Lett et al. and Fazio have defined a stricture as a narrowing that does not allow passage of a 15-mm sigmoidoscope. It is believed that, according to Kyzer and Gordon considered stenosis as any anastomosis that did not accept the 19-mm sigmoidoscope. The aetiology of anastomotic stenosis is not completely understood. When the colon is found to be ischaemic it may lead to further stricture above the anastomosis. It is proposed that stenosis may be caused by insufficient circulation in the marginal artery and this insufficiency may be aggravated also by irradiation. Experimental studies indicate that stapled anastomoses heal by second intention because the mucosa of the bowel segments is not in apposition but is separated by the muscular and serosal layers. Therefore, the precise stapled anastomosis predictably forms a perfect circular scar, which results in a narrowing of intestinal lumen. The stenosis is almost always subclinical and faecal dilatation ultimately provides for wide patient anastomosis [91, 94, 95]. Benign strictures arise in 5.8–20% of colorectal anastomoses. For such strictures, endoscopic dilation has proven to be a useful and safe treatment. Both through-the-scope balloon and over-the-wire pneumatic balloon dilation techniques are effective and safe for treatment of benign colorectal anastomotic strictures. Were et al. also reported good results after dilation of benign strictures following LAR using Savary-Gillard bougies [96, 97]. Yagyu et al. [98] found regular finger dilation of the anastomosis to be useful for preventing anastomotic stenosis after LAR.

The role of temporary defunctioning stoma in patients undergoing LAR remains controversial. Grabham et al. [99] suggest that it should be performed in selective cases where there is a concern about the anastomosis due to difficult dissection, incomplete doughnuts and tension on anastomosis. Machado et al. [100] compared surgical outcome after LAR for rectal cancer with colonic J-pouch at two departments with a different policy regarding the use of a routine diverting stoma. A total of 161 patients with invasive rectal cancers were operated on between 1990 and 1997 with TME and a colonic J-pouch. Eighty patients were operated on in a surgical unit using routine defunctioning stomas (in 96%) whereas 81 were operated on in a department in which diversion was rarely used (5%). There was no difference between the two centres in post-operative mortality in connection with the primary resection and subsequent stoma reversal (3.7 vs. 3.8%). No significant difference could be found in the number of

patients with pelvic sepsis (anastomotic leak: 9 *vs.* 12%). According to this study, the routine use of diverting stoma does not protect the patient from anastomotic complications or pelvic sepsis and requires a second admission for closure.

Another interesting issue concerning LAR is small bowel obstruction as the impact of diversion ileostomy. Poon et al. [101] reviewed 214 patients who underwent LAR between 1993 and 1999 and were readmitted with the diagnosis of small bowel obstruction. Median follow-up was 39 months; 22 patients presented with 30 episodes of small bowel obstruction, and operations were necessary in nine patients (40.9%). Malignant obstruction occurred in two patients (10.3%). Obstruction within 6 weeks of surgery (including closure of stoma) occurred in 13 patients (6.1%). Early obstruction occurred at a higher incidence in those patients who had an ileostomy than in those who did not (9.1% *vs.* 2.9%, p=0.048). The Authors concluded that the presence of diversion ileostomy was associated with an increased incidence of early obstruction; therefore the use of loop ileostomy for proximal diversion should be further assessed.

The goals in the treatment of rectal cancer are cure, local control, and preservation of sphincter, sexual and bladder function. The complications and mortality rate in the setting of pre-operative chemoradiation have not been well defined. However, the results prompted the addition of adjuvant or neoadjuvant pelvic irradiation with or without chemotherapy to reduce local recurrence rates and improve survival rates. Pre-operative radiation therapy results in increased surgical complications and post-operative radiation therapy produces considerable short-term and long-term complications. Enker et al. assessed the pre-operative complications in association with pre-operative radiation. To determine the pre-operative morbidity rate associated with pre-operative radiation sequencing, patients receiving pre-operative chemoradiation were compared with those in the other groups (Pre-op RT n=150; No Pre-op RT n=531). All 681 patients underwent LAR for resection of primary rectal cancer. The type of surgical resection was distinguished between LAR (75%) and LAR with CAA (25%). One third of the patients undergoing CAA were stapled, two thirds underwent perianal sutured anastomoses. The leakage rate was significantly higher in patients undergoing LAR than those undergoing CAA. A temporary diverting ileostomy or colostomy was performed in 214 (31%) patients. Of the patients with a diverting stoma, 122 (57%) had a CAA. The leakage rate was no different among those with diversion or those without. In addition, a diverting stoma did not reduce the incidence of anastomotic leak among those undergoing LAR without CAA. The operative time, estimated blood loss and rate of pelvic abscess formation without associated leak were higher in the Pre-op RT group than the No Pre-op RT group. However, the overall complication rate and incidence of wound infection, anastomotic leaks and pelvic abscess formation not associated with a leak were compared between patients who did and did not receive pre-operative chemoradiation. The incidence of pelvic abscess formation was significantly higher in those who received pre-operative chemoradiation. Because LAR is a clean-contaminated procedure, localised sepsis in the contaminated radiated field is not surprising. It would be of interest to evaluate the potential efficacy of a more prolonged antibiotic course in patients receiving pre-operative radiation [98]. Pucciarelli et al. reported that pre-operative combined RT and chemotherapy for rectal cancer did not affect early post-operative morbidity and mortality in LAR. They respectively compared 41 patients (Group A) with 30 patients (Group B) who in the same period underwent surgery without pre-operative adjuvant therapy. Minor post-operative complications that occurred in both groups (Group A – 51%, Group B – 62%) were anastomotic leak, middle and moderate anaemia, urinary tract infection, urinary retention, post-operative prolonged ileus, wound infection and bronchopneumonia. Major post-operative complications occurred in each group (p=NS). They were anastomotic leak, anastomotic haemorrhage, descending colonic necrosis, rectovaginal fistula, haemoperitoneum and necrosis of gastric curvature, pelvic abscess and high output from ileostomy requiring readmission. Anastomotic leaks were treated conservatively with no further morbidity or reoperation. Of the two patients with rectovaginal fistulas, one underwent ileostomy and the other, who already had a diverting stoma, was given conservative treatment. One patient with an anastomotic haemorrhage was given endoscopically guided sclerosin injections. Three patients required reoperation for post-operative complications: one cirrhotic patient underwent reoperation for necrosis of anastomosed colon; the second patient required surgery for massive bleeding from the sacral veins; and the third one for ischaemic necrosis of the greater gastric curvature requiring emergency gastric resection. Conservative treatment was given for the remaining two major complications: a para-anastomotic abscess and combined water and electrolyte deficit caused by the high output from the covering ileostomy. At multivariate analysis, ASA score 3, absence of diverting stoma, LAR with CAA, low pre-operative haemoglobin value and more intraoperative blood loss were found to be independent predictors of major complications. Whether pre-operative

adjuvant therapy influences early post-operative mortality and morbidity is still controversial. Most of the studies report morbidity and mortality after pre-operative adjuvant RT alone. Some Authors have found significant peri-operative mortality or morbidity rates or both, although others have not [102].

The advent of surgical stapling devices has resulted in a dramatic reduction in the number of abdominoperineal resections, however, transanal stapled anastomosis may be associated with continence disturbances and reduced post-operative anal sphincter function. Disorders of continence are present in up to 60% of all patients who undergo LAR for rectal cancer. It is likely that an anal stretch type of mechanism is responsible for internal sphincter injury that is seen on ultrasound [103].

Although anastomotic staplers are common in surgical practice and they allow more extended, lower resections of the colorectum, complications associated with stapler use have been reported. Anastomotic stricture and leakage is the most common. A unique complication following stapler use is colovaginal fistula during LAR. The management of a post-operative rectovaginal fistula after LAR for rectal cancer is difficult and requires reconstruction of the anastomotic site and fistula. One of the reconstructive operations is the technique using the posterior approach through the vaginal lumen for a high rectovaginal fistula repair. Wang et al. reported 140 patients who underwent LAR with a double-stapled anastomosis for rectal cancer. In 4 patients (2.9%) rectovaginal fistula (RVF) developed as a post-operative complication. The RVF developed gradually from 9 to 128 days after LAR. Authors performed modified transvaginal approach for RVF repair with a diverting colostomy. In all 4 patients, the RVFs were completely eradicated with re-establishment of intestinal continuity and did not recur during the mean follow-up period of 29.5 months [104]. My preferred approach is laparotomy and excision of the anastomosis, and to perform a double-stapled anastomosis again.

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Actuality of Colo-Anal Anastomosis

Gian Andrea Binda, Alberto Serventi

Definition

The definition of colo-anal anastomosis is still under debate. This argument is caused by the difference between the surgical anal canal (included between the anal margin and the levator plane) and the anatomic anal canal (between the anal margin and the dentate line). According to some surgeons, therefore, the excision of the rectum up to the levator plane with anastomosis performed on the surgical anal canal or immediately above it is considered colo-anal anastomosis. Others prefer a more rigorous definition, considering as colo-anal anastomosis a suture at the dentate line and referring to the former as a low or ultra-low colorectal anastomosis [1, 2].

Indications

The indication of a colo-anal anastomosis depends on tumour localisation, locoregional extension, anal sphincter function, the patient's morphology and the surgeon's experience [3–5].

Tumour Localisation

In tumours reaching the anal canal, or located less than 1 cm from the sphincter, abdomino-perineal resection (APR) is often the only curative surgery which can be realised, with the exception of some small tumours which are conservatively treatable: local excision or proctectomy with intersphincteric resection. In the case of tumours located above 2 cm from the ano-rectal junction, it is almost always possible to preserve the anal sphincter with an oncologically correct exeresis. In the case of tumours sited between 1 and 2 cm from the anal canal, to achieve a proper distal clearance, we must resort to an intersphincteric resection. For tumours whose lower pole is less than 5 cm from the anal verge, a distal resection margin of 2 cm is enough [6], as long as a complete exeresis of the mesorectum is performed which caudally ends 2–3 cm from the levator plane.

After Heald et al's basic research on total mesorectal excision (TME) [7, 8] the distal section and anastomosis are performed, therefore, behind the anal canal, making the techniques of low, ultra-low and colo-anal anastomosis more routinary. The colorectal anastomosis is defined as *low* if the rectal stump is over 2 cm long and *ultra-low* if it is less than 2 cm. If a total proctectomy with TME is necessary, this will be followed by a manual or mechanic *colo-anal anastomosis*.

Locoregional Extension

External sphincter infiltration represents the only absolute indication of APR, whereas internal sphincter infiltration may be treated with an intersphincteric resection, giving good functional and oncological results [9].

The existence of an anatomic and functional division between the puborectalis muscle and external anal sphincter allows, in limited experiences, excision of the rectum and puborectalis, preserving the external sphincter [10]. At the same distance from the rectum, a small sized tumour may be treated by conservative exeresis, whereas an APR is advisable to treat more extended cancer. This is not for reasons of local invasion, as there is no study showing a correlation between tumour volume and sphincter infiltration, but mainly for technical reasons of local and nervous dissection.

Preoperative radiotherapeutic overdosage may equally lead to avoidance of a colo-anal anastomosis.

Anal Sphincter Functional Conditions

Before considering colo-anal anastomosis, sphincter function must be assessed. A detailed continence history and physical examination by an experienced surgeon are probably the most predictive evaluations

of post-operative function [11]. An abdominal colostomy is preferable to a perineal colostomy in cases where sphincter function is impaired.

Patient's Morphology

The technical difficulties met during rectal surgery vary considerably depending on the patient's morphology. The association of a considerable obesity and of a narrow and deep pelvis may be of hindrance to the technical realisation of a low or ultra-low anastomosis and make it necessary to perform a colo-anal anastomosis with perineal approach.

Surgical Technique

The abdominal part of the procedure implies a mobilisation of the left colon as in low and ultra-low colorectal anastomosis, both with laparoscopic and laparotomic access, and includes the high ligation of the mesenteric vessels, the mobilisation of the splenic fissure and rectum isolation up to the levator plane.

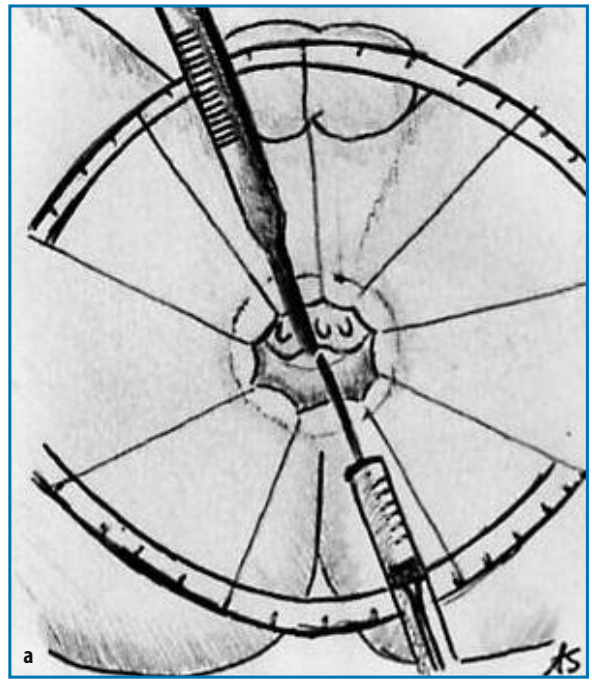
Anastomosis may be performed with different techniques depending on the site of the tumour's lower pole and its degree of invasiveness, the patient's morphology, the surgeon's experience and limitations of flexion of the lower limbs.

Anastomosis Techniques

Handsewn Colo-Anal Anastomosis with Mucosectomy (Fig. 1)

This technique, described by Parks in 1982 [12, 13], is performed with a perineal approach. Once the anal canal has been exposed with a Lone Star® type retractor, rectal mucosa is infiltrated with an adrenaline solution, favouring dissection and haemostasis. Mucosectomy is then performed starting a few millimetres above the dentate line up to the apex of the rectal stump.

The anastomosis is then sutured between the colon or the apex of the colonic reservoir, pulled down to the rectal muscular cuff, and the anal canal with slow absorption stitches [14].



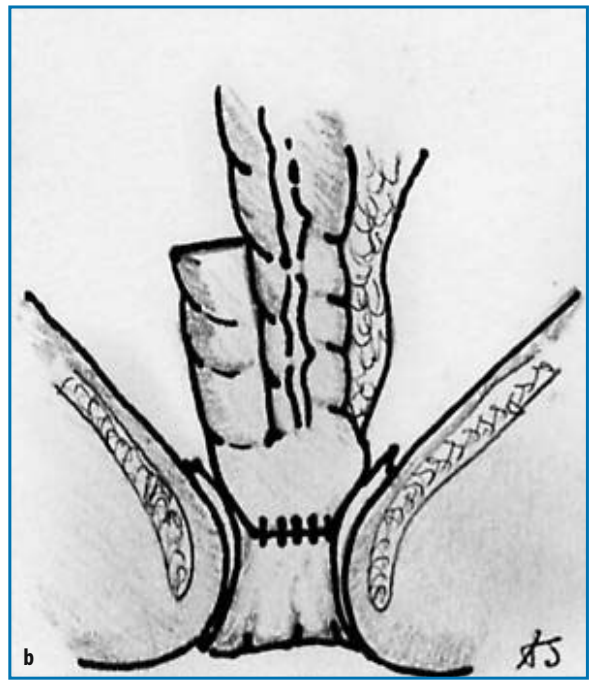


Fig. 1a, b. Park's colo-anal anastomosis

Colo-Anal Mechanical Anastomosis (Fig. 2)

The rectum is sectioned with a mechanical linear stapler at levator muscle level or lower after beginning dissection between the external and internal sphincters. Anastomosis is performed with a circular stapler inserted with a trans-anal approach according to the technique described by Knight and Griffen [15]. The further rectal section determined by circular stapler in some cases may move the anastomosis level to the dentate line realising a "real" colo-anal anastomosis. The functional results improve by associating a colonic reservoir with anastomosis [16].

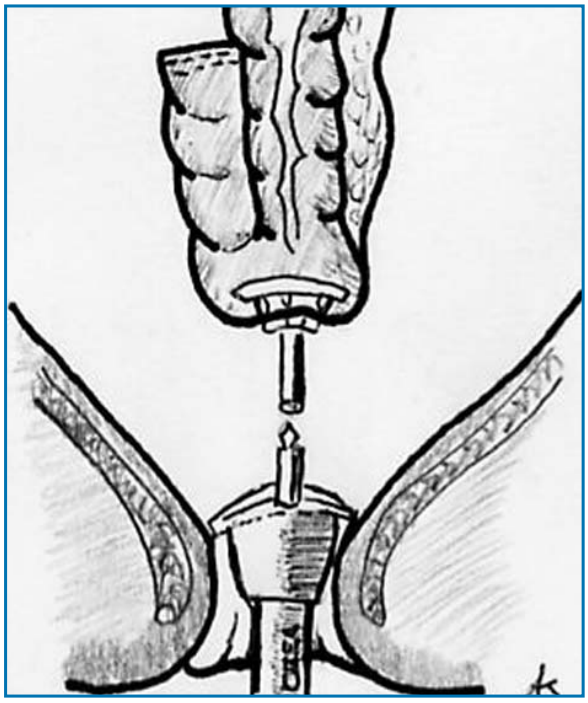


Fig. 2. Colo-anal mechanical anastomosis

Colo-Anal Anastomosis with Rectal Stump Eversion (Fig. 3)

This technique was described by Hautefeuille et al. [17]. The rectal stump, once it has been sutured, is eversed through the anus and sectioned a few millimetres above the dentate line. The colic stump or the reservoir are then pulled down through the anus and the anastomosis is then sutured as before.

In order to allow the overturning of the rectal stump it is necessary to perform the rectum dissection, during abdominal time, as distal as possible. Bowel function is said to be good [18].

Intersphincteric Colo-Anal Anastomosis

This technique, described by Schiessel et al. [19], includes the partial or total excision of the internal anal sphincter [20]. The approach is the same as Park's technique, but the abdominal dissection is more extended, between the two sphincters to a macroscopically healthy area. With a trans-anal approach the intersphincteric plane must be detected and the section performed. A handsewn anastomosis is then fashioned. With this technique it is possible to treat, with a radical intent, tumours located between 1 and 2 cm from levator plane, T1 and even T2, although with a morbidity higher than the ordinary colo-anal anastomosis [21].

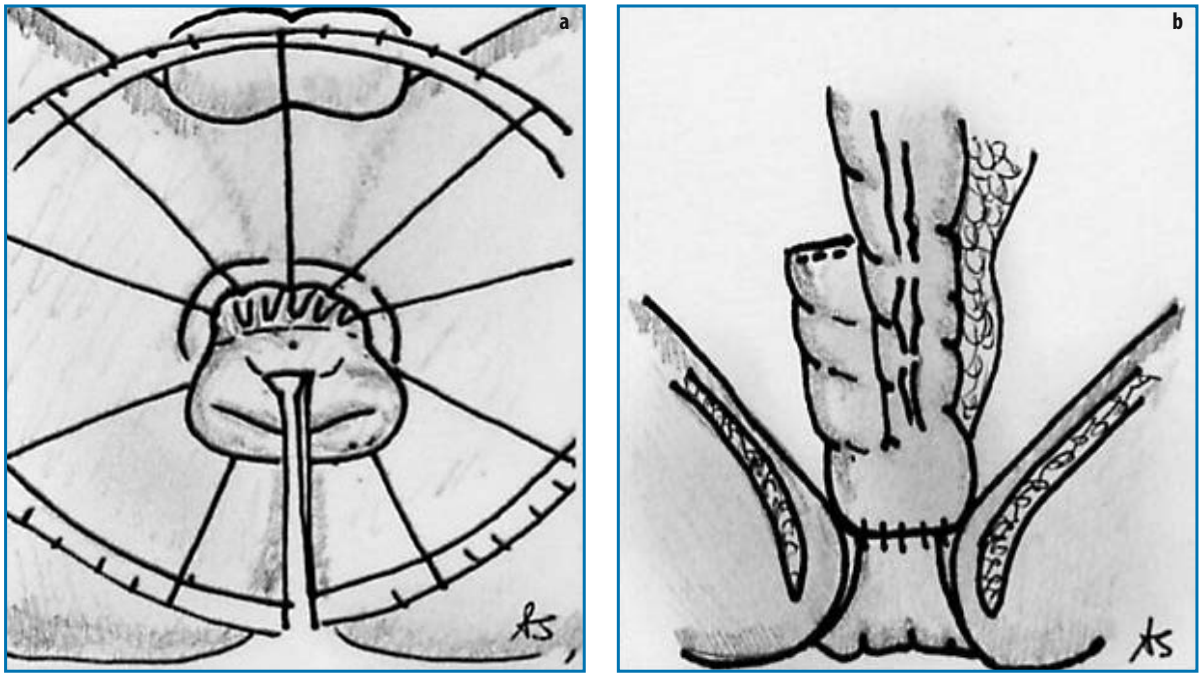


Fig. 3a, b. Colo-anal anastomosis with rectal eversion

Colo-Anal Anastomosis with a Trans-Sphincteric Approach

This technique was described by Lazahortes et al. [22] and combines the abdominal access with trans-sphincteric access according to Mason [23]. The patient is subjected to right lateral decubitus and the left leg is raised to reach a 45° angle. Abdominal dissection is performed as before through an incision to the patient's left side.

Through an incision from the anal margin to the sacrum with coccyx resection. The external sphincter is sectioned to expose the rectum rear side, which is sectioned above the anal canal. Once the anastomosis between the apex of the cholic reservoir and the pectinate line is fashioned, the external sphincter is sutured.

Role of Defunctioning Stoma

The worst complication of colorectal surgery is represented by an anastomotic leak and consequent pelvic infection; the incidence increases after ultra-low colorectal or colo-anal anastomosis, particularly when the exeresis of the mesorectum is complete, due probably to the devascularisation of the residual rectal stump [24].

The incidence of radiologic anastomotic leakage after total mesorectum excision and colo-anal anastomosis is about 16% *vs*. 8% in patients who did not undergo TME [25].

Protective stoma has the purpose of decreasing the consequences of an anastomotic leakage, which not only determines a pelvic peritonitis with a high degree of mortality (about 50%) but causes anorectal fibrotic stenosis [26]. In a recent study of about 2 000 patients, Eriksen et al. [27] presents an incidence of clinical dehiscence of 11.6%, showing that defunctioning stoma not only decreases the consequences of an anastomotic leakage but also reduces the risk of a leakage itself by 60%. Peeters et al. confirms this result and shows defunctioning stoma is related to a lower requirement of surgical reintervention [28]. For this reason a routine defunctioning ileostomy is advised and it may be electively closed after 4–6 weeks.

Results

Oncologic Results

The oncologic results of a colo-anal anastomosis with TME should be compared with the results achieved after anterior resection or APR with total mesorectum excision. The local recurrence ranges in different studies from 6 to 22% and 5-year survival ranges from 64 to 73% [29–32]. These results are comparable with those of the anterior resection and APR [33]. The published oncologic results of colo-anal anastomosis derive from retrospective studies including tumours with heterogeneous histology, different anastomotic techniques, various chemoradiotherapy regimes and different lengths of follow-up, making this comparison of limited significance.

Functional Results

A straight colo-anal anastomosis induces functional disorders in 80–87% of cases. The complete rectum excision implies the loss of its reservoir function determining the *anterior resection syndrome* described by Karanjia et al. in 1992 and characterised by an increased number of evacuations, difficulty with evacuation, incontinence to gas or liquid faeces, night leakage and tenesmus [34]. This syndrome improves significantly after one year [35], but in several studies with long-term follow up, considerable defecatory symptoms persisted. In a study published by Paty et al. [36] with a 4.3-year median follow-up, the most common symptoms patients complained of were: continence disorders (21% incontinence to gas, 23% minor leak and 5% significant leak), evacuation difficulties (32% fragmented evacuation) and 22% of patients reported 4 or more evacuations a day. The results were then classified as excellent for 28% of patients, good in 28% of patients, poor in 32% and very poor in 12% of cases.

To solve this complex mixture of anus and neorectum malfunctions the realisation of a colon reservoir was proposed [31] (Fig. 4), whose physiologic functions are the same as the iliac pouch made for ileo-anal anastomosis. A *J-shaped pouch*, initially 10–12 cm in size, determined serious evacuation problems [37]. Its size was then reduced to 5–6 cm in order to achieve a suitable reservoir without damaging the neorectum function [36]. Several prospective randomised studies proved how the functional results of the colo-anal anastomosis with J-shaped reservoir were much better than the ones made with straight colo-anal anastomosis [39–42]. In Ortiz et al. study [43] on 30 patients, at 1-year follow-up, 38% of patients had normal continence with J-pouch *vs*. 22% of patients with straight anastomosis and the number of evacuations a day was respectively 2 and 4. Hallböök and Sjödahl [44], in a comparative study among patients with J-pouch and a control group, did not find any difference in terms of continence after 1-year follow up; 20% referred evacuation difficulties and needed enemas. When the J-pouch is not feasible because mesentery is too thick or because its insertion into a narrow pelvis is too difficult, it is

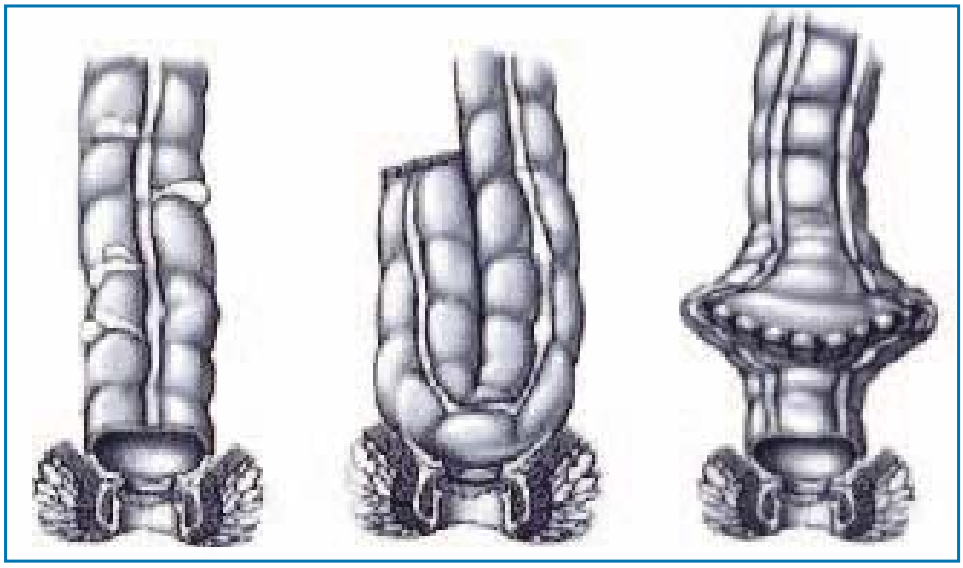


Fig. 4. Straight colo-anal anastomosis, J- pouch and coloplasty

then possible to realise another kind of cholic reservoir: the transverse coloplasty [45]. To perform such a reservoir an 8–10-cm long incision must be made on the colon, at about 4–5 cm from the distal extremity, and be transversally sutured. A prospective randomised study proved that coloplasty gives functional results identical to the ones achieved with J-shaped reservoir [46]. A very recent study by Remzi et al. [47] not only confirms the good functional results achieved by coloplasty, but it also shows a lower percentage of anastomotic dehiscence.

Functional results comparable with those achieved with colo-anal astomosis with J-pouch were reported by Machado et al. [48] in a randomised perspective study on 100 patients, performing latero-terminal colo-anal anastomosis.

Colo-anal anastomosis functional results after intersphincteric resection, with total or partial resection of the internal sphincter, are conflicting in the literature: Holzer et al. [49] reports very good functional results (88% of fully continent patients) whereas a more recent comparative study by Bretagnol et al. [50] shows a higher rate of incontinence and a worse quality of life compared to colo-anal anastomosis preserving internal anal sphincter.

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Role of Colonic Reservoirs in Rectal Cancer Surgery

Felice Borghi, Danilo Donati, Gian Gaetano Delaini, Diego Segre

Introduction

The surgical practice for middle and low rectal cancer has dramatically changed over the past two decades: in most patients undergoing curative resection now the anal sphincter can be preserved with restoration of intestinal continuity, thus avoiding an abdominoperineal excision of the rectum with permanent stoma in about 90% of all rectal cancers, with the same or even better oncological results [1–5].

The development of sphincter-saving procedures, such as very low colorectal or colo-anal anastomoses, has been the consequence of both oncological and technical factors: the improved knowledge of tumour spread, the diffusion of total mesorectal excision with nerve sparing, the development of stapling devices and the impact of neoadjuvant therapy [6–14].

The major advantage of anterior resection (AR) is the avoidance of a colostomy, which means a better quality of life for the patient. On the other hand, the re-establishment of intestinal continuity often results in poor functional outcome as a consequence of an alteration in pelvic physiology. These continence disorders are called "Anterior Resection Syndrome" [15–18].

In order to obtain a decrease of these dysfunctions, techniques alternative to the traditional straight anastomosis were developed, based on the creation of a reservoir able to function as a neorectum.

The aim of this chapter is to analyse the reconstruction techniques with reservoir, their current understanding and to define their clinical role.

Anterior Resection Syndrome

The Anterior Resection Syndrome (ARS) is characterised by continence disorder, ranging from the inadvertent and uncontrollable passage of flatus to frank faecal incontinence, as well as urgency and increased frequency of evacuation. This syndrome may affect up to 90% of patients with straight colo-anal reconstruction and may worsen the quality of life in about 39% of them [15, 17].

The symptoms are more common in the early post-operative period, when post-operative chemotherapy or irradiation are often necessary, and improve progressively within one year.

A combination of factors seems to influence the incidence and the severity of ARS:

- The length of residual rectal stump plays an important role in determining functional outcome after surgery: anastomoses under 4 cm from the anal verge are often associated with a high incidence of ARS [15, 19].
- Patients with anastomotic leakage after surgery show worse anal function as the result of sepsis at the site of anastomosis and pelvic fibrosis [20].
- Adjuvant chemotherapy or irradiation predispose to ARS or can make its symptoms worse [3].
- Pre-operative sphincter function, especially a reduced anal canal mean resting pressure (MRP), can predict patients who may have post-operative continence problems: a comprehensive continence history and physical examination completed by anal manometry and ultrasonography should be recommended, particularly in women, in order to identify cases with high ARS risk [1, 21].

A number of functional studies have been undertaken to identify physiological abnormalities following AR, but several misconceptions about the mechanism underlying ARS still exist.

The urgency and the increased frequency of evacuation can be a consequence of the reduction in large intestinal length and of the denervation of mobilised bowel resulting in a more liquid effluent reaching the anal canal [17].

However, ARS may be also due to damage to the sphincter complex, produced by inserting the stapling device, or the anal retractor, or by injuring the internal anal sphincter during rectal mobilisation, as suggested by significant reduction in anal canal MRP [15, 17].

Other evocated causes of poor clinical function are

the loss of normal anorectal sensation and the reduced rectal capacity and compliance. Manometric studies support this view, showing a reduction of threshold volume (TV) and of maximum tolerable volume (MTV) as well as a persistent absence of the recto-anal inhibitory reflex (RAIR) in 40–70% of cases [22, 23]. As a consequence of the reduced rectal capacity and of the enhanced rigidity of the neorectum, a high-pressure zone is created in the upper part of the anal canal until the sphincter mechanism is overcome. This is confirmed by the evidence that the MTV of the neorectum is inversely correlated to the urgency and the high frequency of evacuation [17, 22].

The idea for the creation of a colonic reservoir, based on the experience of ileal pouches, appeared therefore attractive, especially to increase neorectal capacity and, more recently, also to dissipate the high intraluminal pressure generated within a non-compliant colon.

The procedure that has gained most popularity is the colonic J-pouch reconstruction, although other kinds of reservoirs have been described and some of them are spreading too.

Colonic J-Pouch

The use of a colonic J-pouch following AR was first reported in 1986, when Lazorthes and Parc, simultaneously, described a two-limbed reservoir fashioned from the terminal part of the colon as a J-construction, anastomosed side-to-end to the anus (Fig. 1). This procedure was shown to reduce the dysfunctions associated with low straight anastomosis, especially in terms of stool frequency, by increasing neorectal volume [24, 25]. Since then, the use of colonic reservoirs has been accepted, becoming more and more popular.

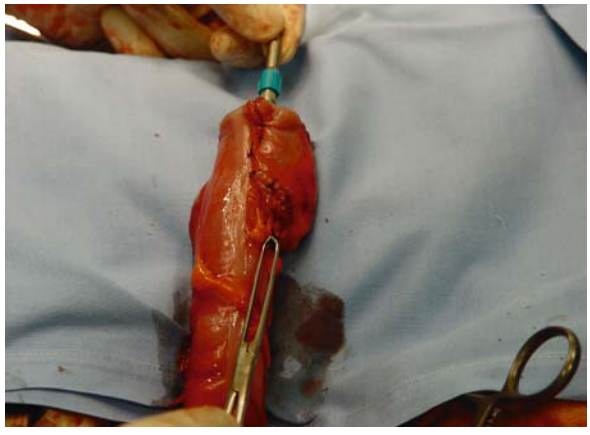

Fig. 1. Small colonic J-pouch of 5–6 cm

Many retrospective studies have shown that the use of the colonic J-pouch is compatible with curative surgery and that the functional superiority of the colonic J-pouch over the straight colo-anal anastomosis is without doubt. All the existing data confirm a functional post-operative improvement after this reconstruction in terms of decrease in the number of bowel movements per day, less urgency in evacuation and, probably, better continence. These studies have provided strong evidence that these patients may not only expect better functional results, but also an improved quality of life in the early months after surgery compared with patients receiving a conventional colo-anal anastomosis. Recent randomised prospective studies confirmed these advantages, especially in the early post-operative period [26–51]. For these reasons, the role of the colonic J-pouch reconstruction in optimising the post-operative outcome of patients after total rectal resection is now widely accepted and it is universally established that J-pouch colic reconstruction is strongly indicated in anastomosis under 4 cm from the anal verge and advisable whenever the anastomosis lies under 8 cm [47–50].

Nonetheless, colonic J-pouches are still not universally used routinely after AR, mainly because there are still several areas of controversy about long-term functional outcome, technical details and functional principles of this reconstruction. In the following paragraphs the data provided in the international literature will be discussed.

Does Colonic J-Pouch Maintain Functional Outcome Over the Long Term?

Whether the benefits are maintained in the long term is still being debated. The data published on the long-term results are contradictory. It is known that bowel function improves with time after a straight anastomosis, presumably as a result of a neorectal neurosensorial adaptation as well as of a recovery of the anal sphincter function. In some studies looking at long-term function after straight and J-pouch construction the incidence of incontinence is equal after the first post-operative year and the frequency of evacuation improves with time in both groups [51, 52]. More recent studies demonstrate, however, that the functional superiority of colonic J-pouch persists over time, even 5 years after surgery, especially in patients whose anastomosis is less than 4 cm from the anal verge [53, 54].

Nevertheless, the superior function within the first post-operative year is clear and this alone can justify

pouch formation instead of straight colo-anal anastomosis in patients with rectal cancer.

What is the Optimal Pouch Size?

The size of the colonic J-pouch is critical as regards the functional outcome. It has been suggested that construction of large colonic J-pouches (10–12 cm), as used at the beginning of the experience, can be the cause of evacuation disorders, characterised by incomplete evacuation or "split defecation" [25, 27, 29, 31, 33, 38, 48].

These problems in several series reach an incidence of 25%, as a probable consequence of the enlargement of the reservoir. Indeed, manometric and pouchographic studies have shown that the colonic pouch increases in size within one post-operative year ("baggy pouch") [55]. The enlargement is substantially greater in a larger pouch and can be also associated to a horizontal inclination of the longitudinal axis ("floppy pouch"), as a consequence of an inadequate expelling force, so that efficient evacuation cannot be achieved [56].

Although evacuation difficulties are a potential drawback of pouch formation, the incidence can be reduced by constructing a smaller colonic J-pouch without offsetting the stool frequency or continence advantages. It is indeed demonstrated that a 5-cm pouch is as good as a 10-cm pouch in terms of functional outcome, avoiding the long-term problems in defecation of the larger reservoirs [44, 57–59].

This finding is noteworthy, as it confirms that pouch function is not a simple mathematical derivative of reservoir capacity.

How Does the J-Pouch Work?

The common understanding of the colon pouch as a neorectum taking over the reservoir function previously performed by the natural rectum cannot on its own explain its functional results. The data discussed before suggest that pouch function is a complex physiological process involving different mechanisms:

- Function of reservoir: faecal contents distend the pouch as a reservoir which increases its capacitance and improves its compliance [38].
- Function of "pressure sump": the pouch is able to dissipate its intraluminal pressure before the MRP of anal canal and the sphincter mechanism of continence are overcome [17].
- Function of motility modification: the functional principle of the colonic J-pouch may be also related to decreased peristaltic waves and motility within the pouch or even to the creation of anisoperistalsis in one limb of the pouch [57, 58].

Which Part of the Colon Should be Used?

Both sigmoid and descending colons have been used to construct the pouch and usually oncological and operative factors determine the choice [43]. The sigmoid colon tract may present three disadvantages: the presence of diverticular disease, a more propulsive motility than the descending colon and a fatty sigmoid mesentery [35, 38].

For these reasons some Authors believe that routine excision of the sigmoid colon is preferable and the use of the descending colon after full splenic mobilisation for pouch construction is the key factor in optimising functional outcome [17, 26].

Which Kind of Anastomosis?

The side-to-end pouch-anal anastomosis can be made either by stapling or by hand suture. Usually the double-stapled technique is preferred, because it is technically simpler and quicker than handsewn anastomosis, which is useful in case of anatomical or technical problems [26, 60].

Is It a Safe Procedure?

Colonic J-pouch anastomosis is a safe procedure and the incidence of clinical anastomotic leaks is lower than in straight anastomosis (0–15% *vs*. 5–27%) for a number of reasons:

- blood supply at the site of anastomosis is improved by using colonic J-pouch, as doppler flowmetry studies show;
- the volume of reservoir reduces the pelvic dead space, preventing pelvic collections and minimising pelvic sepsis [37, 38, 42, 49, 61].

It is not clear whether this reduced leak rate after J-pouch formation is influenced by the increased use of temporary faecal diversion or if anastomotic healing is really improved through benefits of colonic J-pouch reconstruction [26, 62].

Referring to the incidence of anastomotic stricture, no study could find any difference between colonic J-pouch and straight anastomosis groups [48].

Colonic J-Pouch in Elderly People

In the elderly, fear of poor function reduces the indication for AR in favour of abdominoperineal excision

or Hartmann's procedure. The analysis of literature data shows that functional outcome after colonic J-pouch reconstruction is similar in patients older and younger than 75, that the bowel function is comparable in both groups and also that continence is good [17, 48, 63]. These results suggest that the creation of a reservoir is appropriate for elderly patients and, if there are no pre-operative continence problems, it is unjustifiable not to restore bowel continuity.

In spite of these reports, however, the colonic J-pouch did not find widespread use except in specialised colorectal units. Many surgeons are not trained in this technique and prefer a straight coloanal anastomosis, considering the J-pouch reconstruction a complication of AR operation. The failure rate in performing a planned colic pouch is about 26% [64]. The reasons for failure can be divided into two groups: in the first one (86%) are included all technical or anatomic difficulties linked to pouch construction or anastomosis (pelvis too narrow 43%, bulky anal sphincter 33%, extensive diverticular disease 11% and insufficient length of the colon 7%). The second group (14%) contains the relative failures that can follow the surgeon's decision to keep the operation as quick and as simple as possible and perform a straight anastomosis as a consequence of the case complexity (7%) or of the degree of tumour dissemination (7%) [30, 64]. The improvement of this failure rate is the future aim and should stimulate the development of alternative techniques.

Other Reservoirs

Other types of pouch have been evaluated as alternatives for the J-pouch, some remaining isolated experiences and others gaining more consensus.

Ileocaecal Interposition Pouch

Reconstructive techniques based on the interposition of a segment of ileum between colon and rectal stump were proposed in the 1930s [65]. The most popular technique is the ileo-colon-rectoplasty of Jean Quénu. On the basis of these previous experiences, experimental and clinical reapplications of ileal or ileocaecal interposition pouch have been recently described. The ileocaecal interposition consists of the replacement of the excised rectum with a vascularised ileocaecal segment rotated 180° counter clockwise and interposed between sigmoid colon and anus. The principal advantage of this procedure, according to its proponents, is the improved preservation of both extrinsic and intrinsic innervations. Functional outcome and physiological data after this reconstruction appeared comparable to those observed in matched volunteers [66–70].

These kinds of procedures have never been widely accepted and their clinical applications are rare, which is mainly due to their technical difficulties and to the need of additional anastomoses. Moreover, such techniques are not proved to have more functional advantages than the other reservoirs, which, on the other hand, are more easily performed.

Side-to-End Anastomosis

The side-to-end anastomosis, first described in the 1950s, was usually considered the alternative to the end-to-end anastomosis. The advantage of this technique is the optimal blood supply in the site of anastomosis, which is supposed to mean better healing [71, 72].

After becoming less popular as a consequence of the use of stapling devices, it has been recently reintroduced because of the ever-growing reduction of the colonic J-pouch size [73, 74]. Recent studies claim that functional and surgical outcome after side-to-end anastomosis and after colonic J-pouch anastomosis is similar, regardless of whether the reconstruction is performed on the descending colon or on the sigmoid colon [72, 75]. For the functional parameters there were only minor detectable advantages of J-pouch in the immediate post-operative period (stool frequency 2.2 *vs.* 5.4 daily). In order to explain these functional results, retrograde peristaltic waves acting above the anastomotic line from the colic stump have been postulated [73].

According to the Authors, the side-to-end anastomosis is recommended instead of colon J-pouch for technical reasons (narrow pelvis and inadequate bowel length) [72, 73, 75, 76]; however, the only true advantage may be represented by the avoidance of side-to-side anastomosis of the pouch, which makes this procedure faster and cheaper.

H-Pouch

Because of evacuation difficulties after colonic J-pouch reconstruction in spite of the size reduction, a new isoperistaltic colonic H-pouch has been tested, based on the hypothesis that the evacuation difficulties are also a consequence of the anisoperistaltic function of one limb of the J-pouch.

In this procedure, the colon is divided 8 cm proximal to distal colonic section, the distal limb is translated and a 6-cm H-pouch is fashioned with a side-to-side anastomosis. The H-pouch is then anastomosed end-to-end to the anorectal stump.

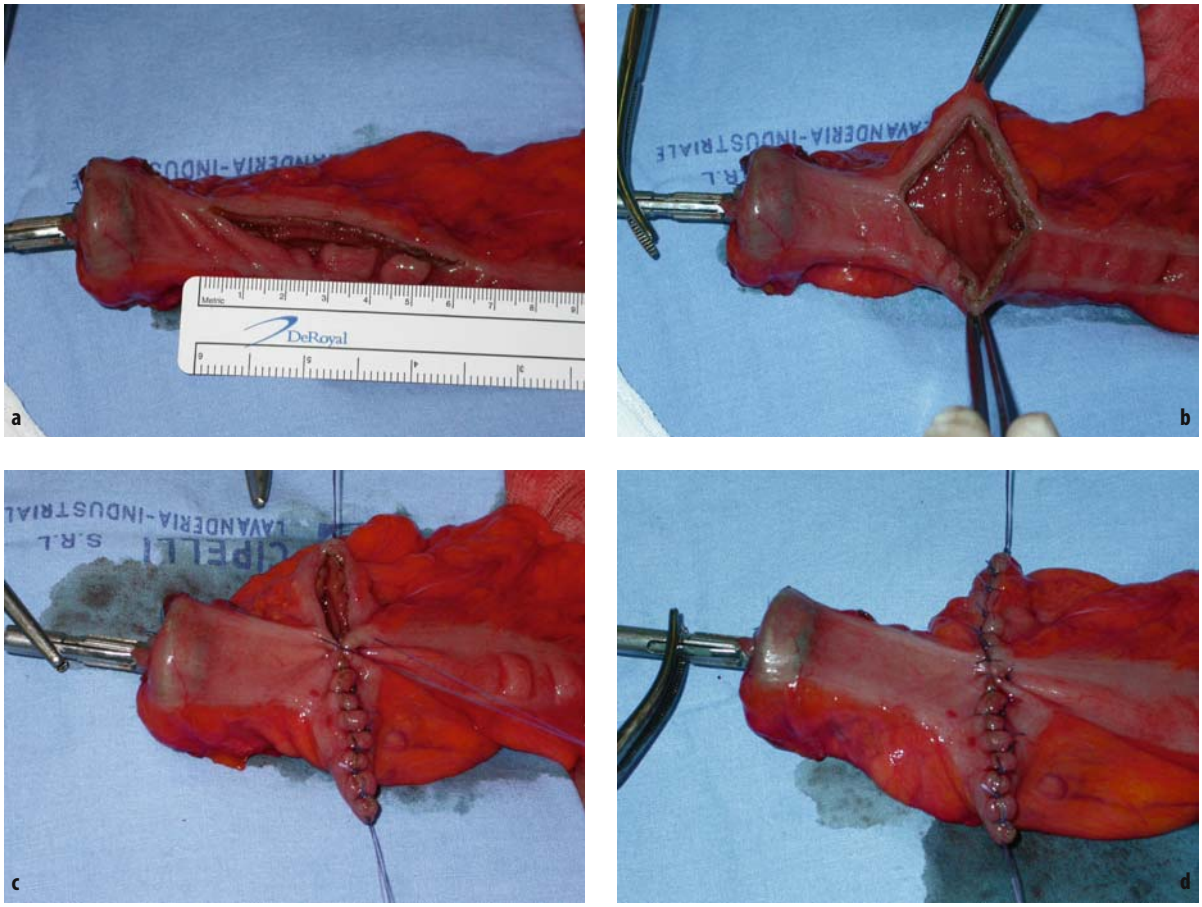

Fig. 2a-d. Transverse coloplasty pouch construction for double-stapled anastomosis: measurement of the longitudinal colotomy and transverse interrupted suture with seromuscular 3-0 polyglycolic acid stitches

The pilot study showed that the creation of this new pouch did not improve the functional results after colo-anal anastomosis compared with the colonic J-pouch, not even in the early post-operative period. In addition, the results did not confirm that an isoperistaltic colonic reservoir could significantly relieve the evacuation difficulties but that, on the other hand, colonic H-pouch was technically more complex to fashion [77].

In short, colonic H-pouch does not provide any benefits over colonic J-pouch and it should not be performed routinely.

Coloplasty

In 1997 another simplified pouch technique, the transverse coloplasty pouch, was introduced to offer an easier alternative to colonic J-pouch. It was based on the findings that a very small colon pouch could reduce the early dysfunctions frequently seen after straight anastomosis and the late evacuation problems associated with a large reservoir. With this technique, an 8–10 cm longitudinal incision is made at the antimesenteric side of the colon between the tenia beginning 4–6 cm from the cut end of the mobilised colon. The colotomy is closed in a transverse manner similar to the closure of a Heinecke–Mikulicz strictureplasty of a small bowel and then an end-to-end stapled or handsewn anastomosis is performed (Figs. 2 and 3) [78, 79].

This technique was first examined in an animal model showing functional results similar to the colic J-pouch reconstruction [80]. The transverse coloplasty pouch was then adapted for use in humans in order to determine results, feasibility and safety of the technique.

From a different published series, patients with coloplasty pouch had less stool frequency, urgency and fragmentation than patients with straight anas-

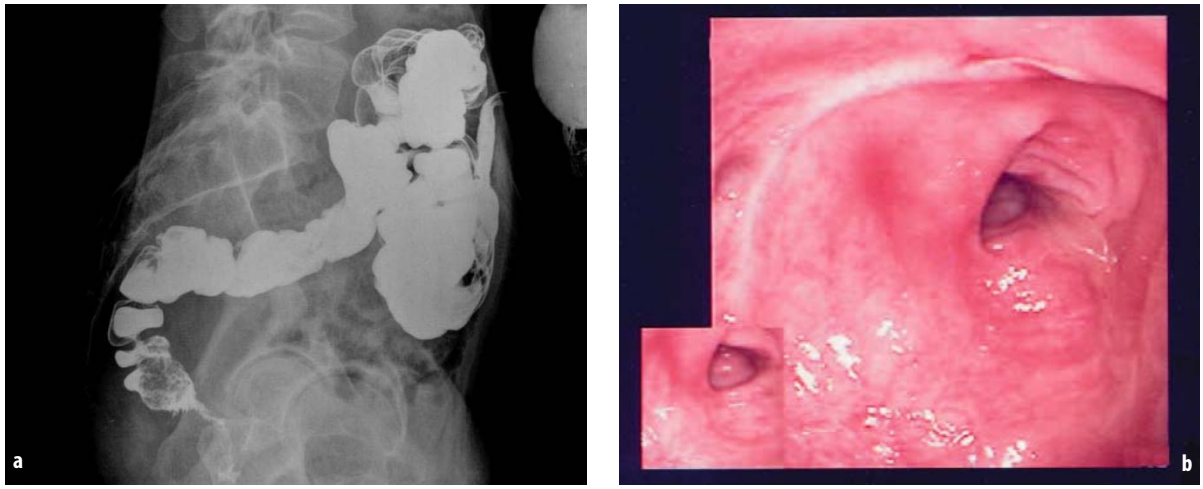

Fig. 3a, b. "Ampulla like" shape of coloplasty in lateral projection of barium enema before ileostomy closure (**a**) and in endoscopic view with the anterior scar of the transverse suture line (**b**)

tomosis. Comparing both coloplasty and colonic J-pouch, the few differences in bowel function did not reach a statistical significance between the groups, each showing in fact a similar functional outcome even in the early post-operative period [79–87]. The rate of intraoperative and post-operative complications was comparable in both groups; in contrast, in one report a significantly higher rate of anastomostic leak (15.9% *vs*. 0%) was evident. All the leaks were at the anterior wall of the colo-anal anastomoses, below the site of coloplasty, although all patients were defunctioned with a loop ileostomy [88].

On the basis of these experiences and our own, we can say about this technique:

- The transverse coloplasty is without doubt technically easier, faster and cheaper than J-pouch reconstruction. It may also be useful when the length of bowel that is needed to reach the anal canal, as well as a narrow pelvis, prohibits the formation of a J-pouch. From the time the technique of coloplasty was adopted, there has been a decrease in the rate of overall pouch construction failure after AR from 26.2% to 5.3%, confirming the feasibility of coloplasty reconstruction [64].
- The transverse coloplasty pouch, compared with a straight colo-anal anastomosis, increases the neorectal volume only by 40% (MTV≤190 ml in our series) [80]; the reservoir function alone cannot justify the improvements of the results of this procedure, especially in terms of stool frequency (in our series mean of daily bowel movements of 2.6 at three months). It is more likely that motility factors, such as disruption of the colonic propulsion as a result of the colotomy on the antimesenteric surface, play a more important role [81, 83].
- The data of high incidence of anastomotic leaks after coloplasty were thought to be a consequence of a compromised blood supply at the anastomosis site as a result of the colostomy [88]. However, laser Doppler studies conducted on animal models did not show any evidence of relative anastomotic ischaemia and other clinical studies do not confirm these findings (Table 1) [80].

In short, the data published so far make it apparent

Table 1. Data from coloplasty's series

Literature data	Anastomotic leaks (%)	Defunctioning ileostomy (%)	Neoadjuvant therapy (%)
Z'graggen et al. [79]	7	100	19
Mantyh et al. [81]	5	65	30
Ho et al. [88]	15.9	100	0
Fürst et al. [82]	–	75	15
Pimentel et al. [83]	13.2	100	33
Köninger et al. [84]	20	84	64
Personal experience, 23 cases	4.3	100	87

that transverse coloplasty constitutes a useful alternative to the colonic J-pouch and that its technical simplicity is the main advantage.

However, in order to understand the real role of transverse coloplasty it is essential to have a longer observational interval study after surgical operation than the published series reported so far have. Indeed, it is to be expected that coloplasty, as well as the colonic J-pouch or straight anastomosis, undergo functional changes over time: in fact the phenomenon of "split defecation" in the J-pouch usually appears or worsens 12 months after the operation.

Conclusions

Patients with cancer located in the lower half of the rectum have been increasingly offered total mesorectal excision preserving the sphincteric mechanism; the oncological results in terms of recurrence and survival rates are comparable to those of abdominoperineal excision. In cases of reconstruction with reservoir, functional results improved with respect to conventional straight anastomosis. However, many studies are retrospective, or different in study design and evaluation methods, or are not comparable in technical details of reconstruction (size of reservoirs, level and kind of anastomosis, use or not of defunctioning stoma etc.) and follow-up intervals. Furthermore, the results from manometric studies are not always correlated to the real clinical outcome of the patients and the functional criteria are often not uniformly defined. So, the data from the current literature are not suitable for direct comparison and large randomised controlled studies should be carried out to definitively define the role of reservoirs.

However, evidence supporting colonic J-pouch reconstruction has been now sufficiently accumulated and the conclusions are that a small colonic J-pouch of 5–6 cm should be preferred to the straight anastomosis in all cases of low or ultralow AR. Adequate pre-operative investigation of the anal sphincter should prevent failures and support the surgeon's decision to perform a restorative procedure with reservoir. The improvement with colic J-pouch reconstruction is apparent in the early post-operative period and probably remains superior to straight anastomosis for 1–2 years after surgery. This is important especially in the elderly, who often have impaired sphincter function, and for those with limited life expectancy when it is desirable to achieve optimum results as quickly as possible.

The side-to-end anastomosis and the transverse coloplasty represent a useful alternative to the colonic J-pouch and their preliminary functional results seem to be superior to a straight anastomosis and very similar to those of a small colonic J-pouch, confirming that the principles of their functioning are not related only to the creation of a neorectal reservoir but also to decreased motility.

Side-to-end anastomosis and, mainly, transverse coloplasty give some technical advantages in reservoir reconstruction and anastomosis. Coloplasty probably represents the ideal compromise between straight anastomosis and short J-pouch, designed as a pouch of small volume without an anisoperistaltic segment. Further studies and longer follow up may reveal other features in this technique.

For these reasons, our personal advice, based on published data available at present and our experience and clinical practice in the last few years, are the following:

- A reconstruction with reservoir, either J-pouch or coloplasty, should be used whenever the anastomosis is under 5 cm from the anal verge and also in elderly patients or those with advanced tumour.
- Transverse coloplasty is indicated in cases of a very narrow pelvis, obese patients with fatty mesentery or when the colon available is not long enough to perform a J-pouch.
- This technique should certainly be preferred in cases of transanal handsewn anastomosis because of its configuration, allowing to cross the sphincteric complex and perform a comfortable direct anastomosis more easily than a colonic J-pouch or a side-to-end reconstruction.
- Although waiting for more data, we recommend at all times the use of a defunctioning stoma to protect anastomosis in case of reconstruction with coloplasty.

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Functional Results of Sphincter-Preserving Operations for Rectal Cancer

Gian Gaetano Delaini, Marco Scaglia, Gianluca Colucci, Leif Hultén

Introduction

Carcinoma of the upper third of the rectum is almost invariably treated with resection and end-to-end anastomosis (high anterior resection). The operation is followed by an excellent functional result. In the last few decades an increasing number of sphincter-saving procedures in rectal cancer cases have been performed. Anterior resection, popularised by Dixon in the 1940s, was the first operation to enable patients with rectal cancer to avoid a definitive stoma. The transanal colo-anal anastomosis extended the possibility of sphincter preservation to patients with very low rectal cancers as well. However, during the last few years there has been a striking change in attitude in favour of an increased use of sphincter-saving operations. The reasons for this altered approach is partly that a safety margin of 4 cm or more distal to the growth is no longer always considered necessary. Technical advances facilitating the construction of reliable anastomoses in the deep pelvis had an important role. After low anterior resection (LAR) such an anastomosis can now be accomplished by a stapling device, permitting automatic suturing in the deep pelvis (Fig. 1). Besides an abdominosacral resection or an abdominotransphincteric resection, the abdominotransanal resection with a hand-sutured colo-anal anastomosis, used mainly by a few experts, is a further possibility for very low tumours [1] (Fig. 2). An important question is if the change in policy might adversely affect the ultimate cure of the disease, a question that has still not been definitively answered. Another question is whether the functional results are acceptable after this type of surgery.

Anorectal function deteriorates following low colorectal/colo-anal anastomoses and stabilisation of functional results may require 1–3 years in the majority of patients [1–3]. During this period, frequency and fragmentation of stools, the feeling of incomplete evacuation, tenesmus and urgency are common complaints. Faecal continence may account for 13–80% of cases [4, 5]. Usually, in these cases,

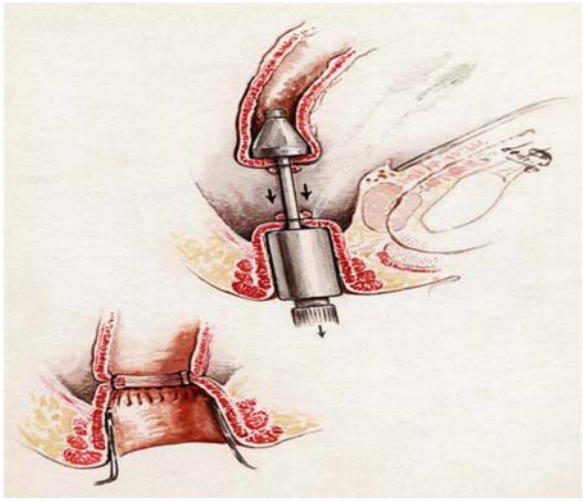

Fig. 1. Schematic illustration of a low anterior resection with a stapled recto-anal anastomosis

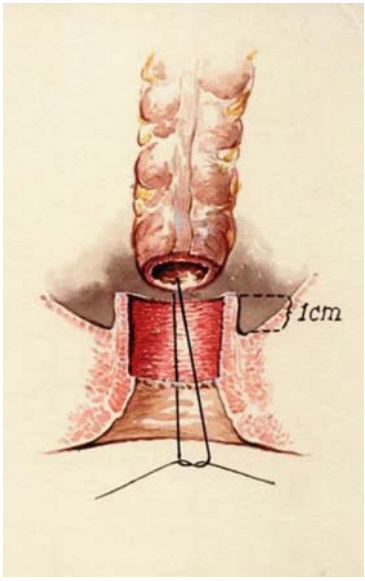

Fig. 2. Schematic illustration representing a proctectomy and reconstruction of bowel continuity with a hand sutured colo-anal anastomosis

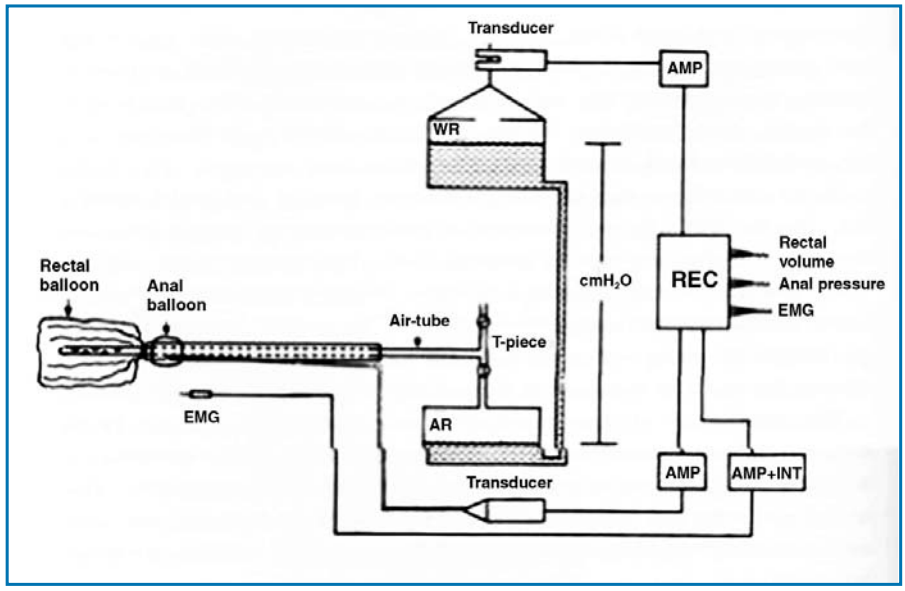

Fig. 3. Manovolumetry performed according to a previously described method [34] allows the investigation of the neorectum volume. Volume and contractility are recorded during the graded isobaric distension of a flaccid plastic bag placed within the neo-rectum. Volumes are defined as the peak volume reached during a distension of 40 cm H_2O, which is maintained for 60 s. Resting and maximal squeeze pressures are recorded by means of cylindrical water-filled cuff

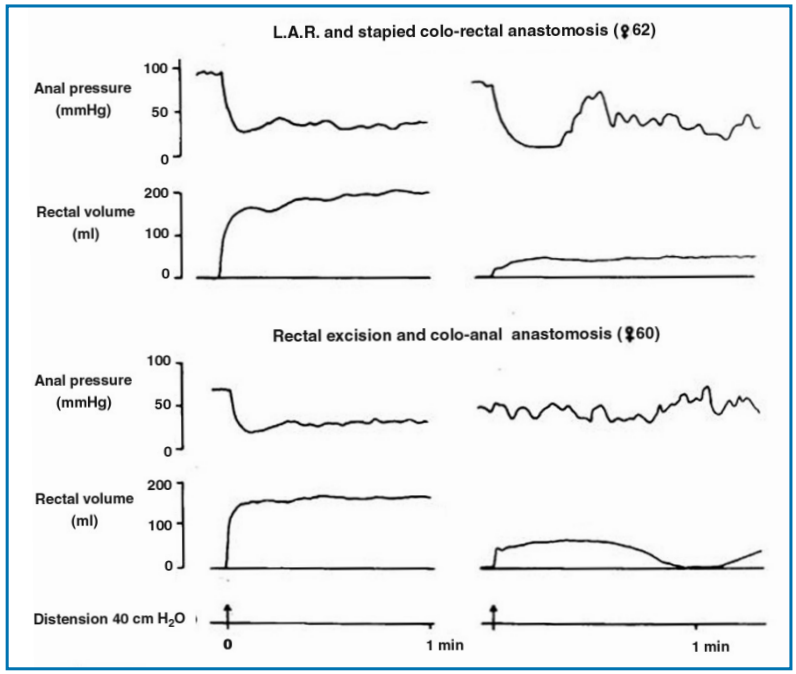

Fig. 4. Example of manovolumetry of a low anterior resection (LAR), before operation (*upper panel, left image*) and after the covering stoma closure (*right image*). Post-operative rectal volume is significantly reduced, there are involuntary contractions of the external sphincter and the recto-anal inhibition reflex (RIRA) is present. On the *lower panel*, a manovolumetry in a case of low rectal cancer before (*left*) and after (*right*) low anterior resection and straight colo-anal anastomosis is shown. The rectal volume is reduced to a third; when an involuntary rectal contraction appears, the reservoir function seems completely lost. This aspect coupled with a weak sphincter pressure might explain the post-operative faecal incontinence, which was complained of by the patient. Moreover the RIRA disappears and threshold for urgency increases

alterations of continence are limited to impaired control of flatus, soiling, occasional loss of liquid and sometimes, solid stools.

Causes of Post-Operative Disordered Defecation

Loss of the Rectal Reservoir

Experimental studies with balloon distension have shown that the rectum is much more sensitive and discriminating than the colon. However, several studies have shown evidence that a colonic segment brought down in the pelvis to restore continuity after complete rectal excision acquires an imperfect sort of rectal sensation thought to depend on receptors in the pelvic floor muscles. Pelvic sepsis and resulting fibrosis renders such activation more difficult and may explain the unsatisfactory functional results after such a complication. Studies in animals have shown that there are specific relaxatory fibres in the parasympathetic pelvic nerves, which might explain the unique ability of the rectum to accommodate a sustained distension. This phenomenon is illustrated in Figure 4

showing the effect of continuous rectal distension on rectal volume and anal pressure before and after surgery (own experience). Before surgery, rectum slowly expands to accommodate the balloon used for distension. In contrast, the post-operative recordings are characterised by a low volume and marked recurrent volume decreases (i.e., contractions). Such vigorous contractions might explain why some patients are incontinent despite normal anal pressures.

Anal Resting Tone and Squeezing Capacity

The reported effects of sphincter-saving operations on the internal anal sphincter (IAS) are contradictory. Goligher et al. [6] showed a very low resting pressure in patients with a short rectal stump (6 cm or less) corresponding to the levels recorded in patients with idiopathic faecal incontinence. In contrast, recent studies have demonstrated only a slight reduction or even normal resting pressure both after LAR and transanal resection. The external sphincter, responsible for voluntary contraction, appears to be unaffected after these procedures.

Recto-Anal Reflexes

External sphincter contraction in response to rectal distension can be evoked in sleeping subjects, protecting against leakage of the rectal contents as the IAS relaxes. Prolonged distension is followed by inhibition. As judged by EMG recordings, the reflex is intact both after LAR and colo-anal anastomosis.

Rectal Distension Inhibits Resting Anal Sphincter-Tone

This decrease in tone allows the rectal contents to reach the sensitive anal mucosa, allowing a distinction between gas, fluid and faeces. Goligher et al. [6] suggested that at least 6–8 cm of intact anorectum is necessary for maintenance of an intact recto-anal reflex. This assumption has been challenged by Lane and Parks, who showed the response in 9 out of the 12 patients after colo-anal anastomosis, some of them only after more than one year had elapsed, however. The reappearance of the recto-anal inhibitory reflex, which has also been observed in one of our series of patients, might at least partly explain the subjective improvement occurring as late as one to two years after surgery.

Many of the undesirable consequences of anterior resections and straight low rectal or colo-anal anastomoses are believed to be due to loss of the rectum's reservoir capacity [7], but other significant factors are the effect of radiotherapy, septic complications, trauma to the sphincter complex and the damage of nerve pathways.

The influence of different factors on functional results will be considered in the following paragraphs.

Restoration of Intestinal Continuity After Sphincter-Preserving Resection

To compensate for the loss of the reservoir function, in 1986 Lazorthes et al. [8] and Parc et al. [9] presented their results with a colonic J-pouch as a neo-rectal reservoir. Since then a number of studies have been performed to assess the functional outcome of the colonic J-pouch and to compare the results with those of straight anastomoses [4, 8]. It has been shown that patients with the colonic J-pouch present a better adaptation (Figs. 5–7) and significantly better function in terms of frequency of defecation, presence of stool fragmentation, urgency, diarrhoea and incontinence [4]. It has been further demonstrated that the optimal dimensions for the colonic J-pouch are between 6 and 7 cm, with a maximum of approximately 8 cm. Smaller pouches are associated with a reduced reservoir function, whereas larger ones are associated with evacuation difficulties [10]. The incidence of symptomatic anastomotic leakage seems reduced because the colonic J-pouch has a superior blood flow at the proximal bowel end as compared to the straight colo-anal anastomosis [11]. Neither the functional superiority nor the improved safety of the colonic pouch following a colo-anal anastomosis appear to have been challenged so far, however it has been speculated that the advantage of

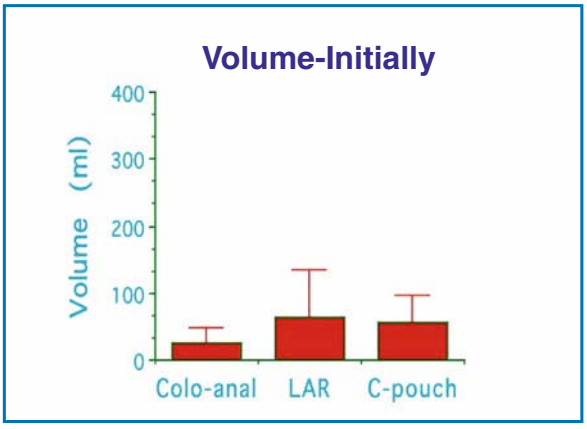

Fig. 5. Early post-operative neo-rectal volumes after three different rectal reconstructions

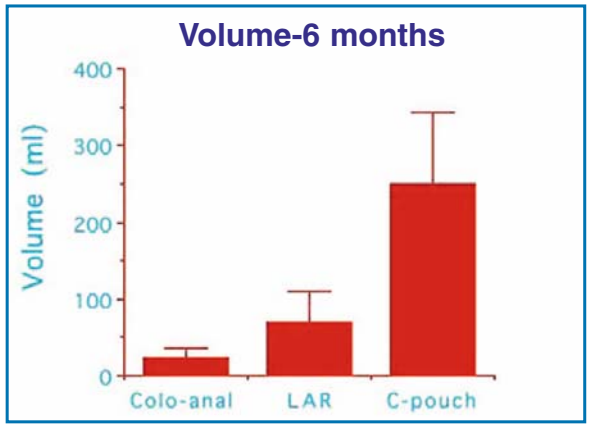

Fig. 6. Favourable expansion of the rectal reservoir of a colo-anal pouch anastomosis as compared to a straight colo-anal and low anterior resection

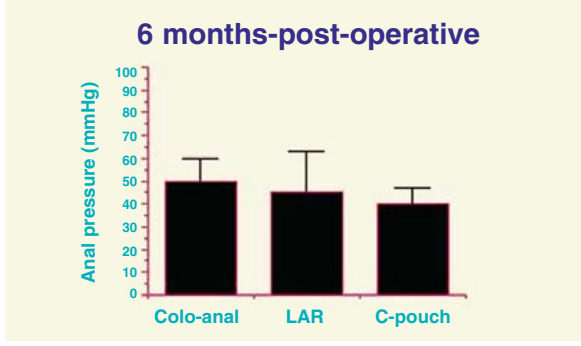

Fig. 7. The anal pressures after the three different rectal reconstructions show no significant differences

the colonic J-pouch is not in the creation of a larger neorectal reservoir but, rather, may be related to decreased motility [12]. Therefore a new surgical concept for rectal replacement is the transverse coloplasty pouch [13]. The early functional outcome is favourable and can be compared to other colonic reservoirs. The concept of reducing early dysfunction seen after straight colo-anal anastomosis and avoiding long-term problems of pouch evacuation is supported by more recent findings [14].

Functional Outcome After Intersphincteric Resection of the Rectum

Resection of the upper third of the anal sphincters may allow even lower tumours to be safely resected without abdominoperineal resection; the transection of the bowel wall possibly with partial resection of the upper anal canal including the IAS is carried out. This intersphincteric resection was based on the original Parks technique, which involved complete removal of the rectum [15]. Initial results suggested that there are minimal adverse effects on post-operative continence [16].

Intersphincteric resection can also provide tumour-free margins for very low rectal tumours, and can be recommended in patients who are candidates for abdominoperineal resection aiming to avoid a permanent colostomy [17]. However, the IAS is resected sometimes with an additional partial external sphincter resection that leads to impaired post-operative continence, with approximately a quarter of patients incontinent to solid stools and half of them with incontinence to liquid stools at least once per week [18]. Functional outcome might be improved with a colonic J-pouch [18] or by a smooth muscle plastic technique [19].

A recently developed EMG signal detection and analysis tool [20] can provide information about the electrophysiology of anal sphincter muscles and computer-simulated motor unit action potentials (MUAPs) (Fig. 8). The EMG anal probe allows the acquisition of EMG from several locations around the anal canal and at different levels from the anal verge. As shown in Figure 9, after intersphincteric resection a reduction of bioelectric activity of the external sphincter could be observed, suggesting damage caused to this muscle during the dissection.

Pre-Operative Radiotherapy

Pre-operative radiotherapy in rectal cancer has a definite role: it results in tumour downstaging and allows an increasing number of cases of sphincter-preserving surgery in low tumours [21]. However, it may result in impaired post-operative continence and increased frequency of defecation. This has been attributed to radiation injury to the sphincter and distal rectum. Exclusion of the anal sphincters from the field of radiation and reconstruction using colonic pouch-anal anastomosis has been shown to minimise post-operative dysfunction [22].

Outcome After Pelvic Sepsis and Post-Operative Radiotherapy

Pelvic sepsis and post-operative radiation therapy can cause an earlier onset and more pronounced functional disturbances as well as a longer period of adaptation. Both conditions can determine an irreversible fibrosis of the anastomosis and of perianastomotic, pericolic and pelvic spaces and a direct, persistent injury to the neorectum and anal sphincter

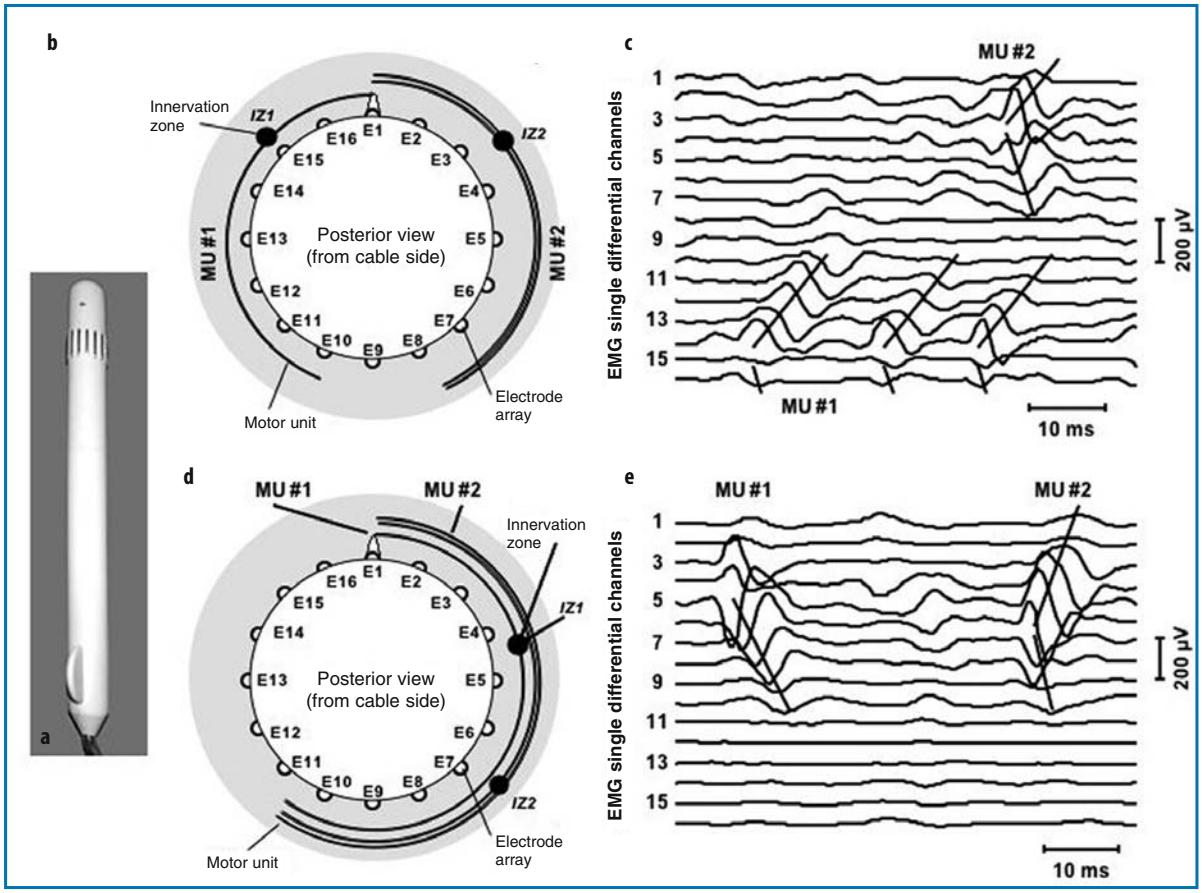

Fig. 8a-e. a Anal probe used for the EMG acquisitions. The probe carries an array of 16 silver electrodes equally spaced along a circumference. **b** Representation of the anatomical configuration of the external anal sphincter of a female subject at 1 cm inside the anal orifice. Such configuration was obtained after a visual inspection of the EMG signals shown in **c**. **c** EMG signals detected with the anal probe at 1 cm depth inside the anal orifice of a female subject. **d** Representation of the anatomical configuration of the external anal sphincter of a male subject at 1 cm inside the anal orifice. Such configuration was obtained after a visual inspection of the EMG signals shown in **e**. **e** EMG signals detected with the anal probe at 1 cm depth inside the anal orifice of a male subject. The different architectures of the muscles are evident. Case **b** shows a sphincter with innervation in both hemi-sphincters, while case **d** shows a sphincter with innervation in only one hemi-sphincter. In case **b** damage of one innervation zone would make the sphincter asymmetric, while in case **d** damage of the innervation zone would likely denervate the sphincter and result in incontinence. Very large interindividual variability has been observed. No standard innervation pattern has been found [20, 35]

complex, leading to a longer standing presence of symptoms. Post-operative pelvic radiotherapy has significant adverse effects on anorectal function, with higher rates of clustering and frequency of defecation than with pre-operative radiotherapy [23]. In case of post-irradiation incontinence, the tendency of stools to be liquid for concomitant ileal injury may further aggravate the situation [24]. Stoma closure is not always possible in patients who experienced anastomotic leakage and, in those who have the stoma closed, impaired long-term anorectal function has to be expected. Evacuation problems with reduced neorectal capacity during manovolumetry (Fig. 3) have been shown [25].

Other factors contributing to the determination of functional disturbances are damage to innervations and trauma to the residual rectal stump and sphincter complex resulting from the wide dissection of perirectal structures [26]. Nerve damage occurs in the superior hypogastric plexus and in the inferior mesenteric plexus during aortic bifurcation dissection manoeuvres, at the inferior mesenteric artery and superior haemorrhoidal artery during the manoeuvres of isolation and section of the mesorectum [27].

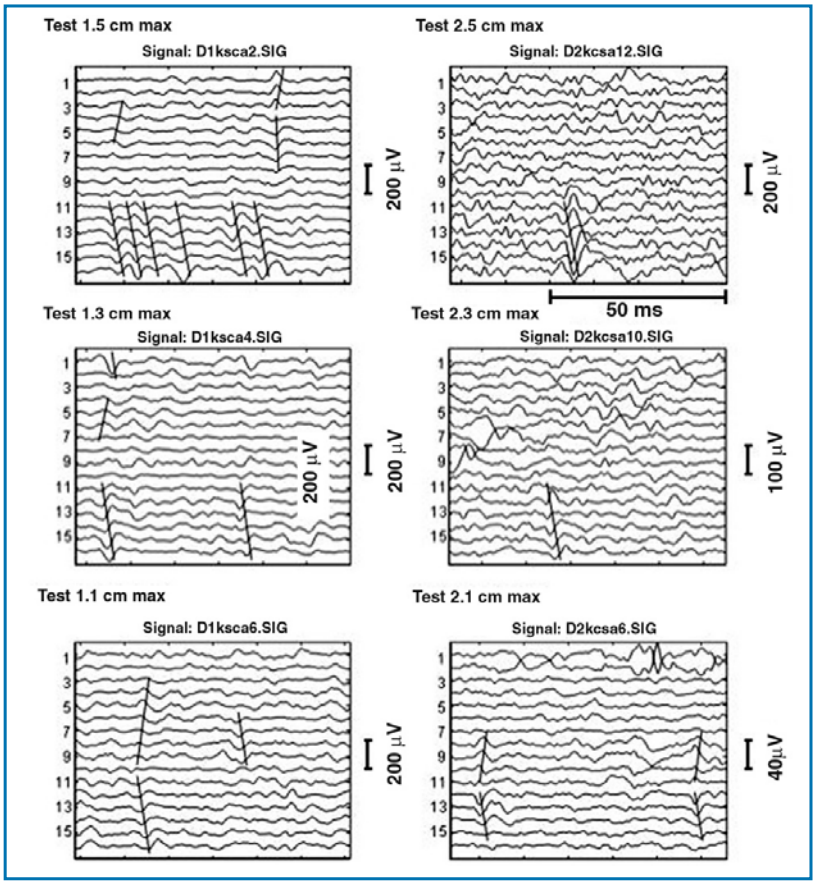

Fig. 9. Patient tested before and 14 days after intersphincteric resection for low rectal cancer (4 cm from the anal orifice); major faecal incontinence at the moment of exam. Signals were acquired at three levels from anal verge during maximal voluntary contraction, performed before (Test 1) and after (Test 2) intersphincteric rectal resection. Signal amplitude is lower at 3 cm and 5 cm from the anal verge in the post-operative test, while the EMG activity at 1 cm appears to be similar in both investigations. Few motor unit action potentials (MUAPs) are visible at 5 cm depth over channels 1–8 (right hemi-sphincter) in the signals acquired during the second test, while higher EMG activity in the same region was evident from the first test. This reduction of activity could be due to the intersphincteric resection performed to remove the rectal cancer. (Courtesy of Prof. Merletti R LISiN (Laboratory for Engineering of the Neuromuscular System, Torino, Italy)

Genitourinary Function After Sphincter-Sparing Surgery for Rectal Cancer

Injury to the pelvic nerves usually results in mixed sympathetic, parasympathetic and pudendal nerve impairment. The most common manifestation of this disorder is a failure to void following removal of the urethral catheter and the development of painless urinary retention. The condition is often misdiagnosed as prostatic obstruction in men or "psychogenic" retention in women; caution should be used before resorting to transurethral surgery in either of these circumstances. Further outflow resistance may not only fail to produce normal voiding, which is the result of the damage to the parasympathetic innervation of the detrusor rather than outflow obstruction, but also may further damage an already neuropathic distal sphincter and precipitate urinary incontinence.

In an attempt to reduce the incidence and the severity of these disturbances, "nerve sparing" resection techniques have been developed, aimed at avoiding damage to the nervous plexus.

Sexual Dysfunction Following Mesorectal Resection for Cancer

Surgery for rectal cancer may decrease the sexual function but the introduction of total mesorectal excision (TME) with autonomic nerve preservation has significantly increased the number of men with preserved post-operative sexual function [28]. In a prospective study of sexual function before and after rectal cancer surgery, TME significantly preserved the ability to achieve orgasm and to ejaculate when compared to standard rectal cancer surgery [29]. In a retrospective evaluation of sexual function following TME, 86% of patients less than 60 years of age and 67% of patients older than 60 years maintained their ability to engage in sexual intercourse, while 87% of all men maintained their ability to have an erection following TME. Retrograde ejaculation occurs rarely but does not diminish the patient's capacity for normal sexual activity [30]. The effects of TME for rectal cancer on female sexual function are less clear.

One study reported maintained female sexual function, with 85% experiencing vaginal lubrication

and 91% achieving orgasm [31]. A higher proportion of women patients report sexual inactivity or indifference prior to surgery, resulting in greater difficulty in an accurate evaluation of their post-operative status [28].

Effect of Laparoscopic Technique on Genitourinary Function

A recent study [32] investigated the frequency of bladder and sexual dysfunction, secondary to pelvic nerve injury, following laparoscopically assisted and conventional open mesorectal resection for cancer in a randomised trial of laparoscopic *vs*. open resection. A retrospective analysis of bladder and sexual function before and after operation was performed by means of postal questionnaires and telephone interviews. Of the responders, 40 patients had undergone laparoscopically assisted resection and 40 had had an open operation. No significant deterioration in bladder function following an operation was observed, although two patients in the laparoscopic group required long-term intermittent self-catheterisation. A significant difference in male, but not female, sexual function was noted, with seven of 15 sexually active men in the laparoscopic group reporting impotence or impaired ejaculation, compared with only one of 22 patients having an open operation. All patients with bladder or sexual dysfunction in the laparoscopic group had resection of either bulky or low rectal cancers. It was therefore suggested that laparoscopically assisted rectal resection is associated with a higher incidence of male sexual dysfunction, but not bladder dysfunction, than the open approach. This has implications, particularly for sexually active males with bulky or low rectal cancers, when deciding the best operative approach.

Other continence-related problems can occur after restorative rectal cancer surgery or any type of low anastomoses due to the use of the circular stapling device. In fact the passage of the stapler through anal sphincter can cause a stretching of anal sphincter and consequent injury. By comparison, the overall results reported in recent series with stapled anastomosis appear to be more favourable than those obtained after handsewn anastomoses. The reason that function would be better with the use of a stapling technique is obscure. However, in the early series the rate of anastomotic dehiscence and pelvic sepsis was higher than in series of later years and it is probable that such complications influence the results adversely. As regards direct trauma to the sphincter complex, anal dilatation performed during these surgical procedures is a frequent cause of incontinence, particularly in patients submitted to a forceful finger dilatation [32]. A forceful dilatation of the external sphincter and puborectalis muscle results in profound and persistent fall in anal canal pressure [2] and it has been associated with severe damage to the IAS on anal ultrasonography [32]. Another factor might be that the criteria of selection probably vary in different samples as indicated by a varying mean age of the patients. In our experience the functional results after LAR are far from satisfactory when analysed in an unselected samples. During the first month the majority of the patients suffered from increased frequency, pronounced urgency and a good deal of incontinence for faeces and flatus. Although the function gradually improved during the course of one year, about 50% of our patients had permanent disturbances of continence.

Finally, low colorectal or colo-anal anastomoses determine a new anatomical shape of the pelvic region characterised by an increase of the anorectal angle. This condition, in association with the other mentioned factors, is able to cause more or less marked post-operative incontinence. A further factor that could interfere with continence control is the integrity of the anal canal mucosa with loss of the discriminatory sensitivity between flatus and stools. Pathophysiologic studies into colo-anal and ileoanal anastomoses with or without mucosectomy [33] would demonstrate that the absence of the mucosa does not influence the anal canal sensitivity threshold significantly, provided that the sphincter anatomic and functional integrity and reservoir function are preserved.

Criteria of Selection

The modern techniques with low stapled anastomosis or colo-anal anastomosis apparently give rise to better functional results than the handsewn anastomosis or the pull-through operations used in the 1960s. Nevertheless, even in the hands of the experts, there are still long-term failures and a function which is ultimately acceptable is often preceded by severe disturbances. Therefore the criteria of selection should be carefully assessed.

Tumour Type

In view of the distressing disturbances during the first post-operative year, a sphincter-saving operation involving a low anastomosis has very doubtful merits when life expectancy is short. Thus, in a patient with a low rectal carcinoma and distant metastasis, a well functioning abdominal colostomy probably offers a better quality of life. Moreover,

although the radicality of the operation is probably equivalent to that after abdominoperineal excision, the development of a local pelvic recurrence will give early and distressing symptoms, which requires abdominoperineal excision. Unfortunately this operation, if possible to perform, will seldom be curative. Therefore a restorative operation for a low-sited rectal cancer should be reserved for mainly limited growths with low-grade malignancy. Endo-anal anastomosis should only be considered for small tumours where adequate distal clearance cannot be obtained even by stapled low anterior resection.

Bowel Function

Frequency and urge to defecate, overwhelming a fairly normal sphincter musculature, appear to be the main cause of incontinence after sphincter-saving operation. Therefore the prospect of a good functional result is better in a patient with 2–3 bowel movements/week than in a patient with frequent movements. A history of irritable bowel syndrome, diverticular disease and chronic diarrhoea (stool weight >200 g) are other factors going against restorative surgery.

Sphincter Function

It is obvious that a patient with a history of anal incontinence should not be offered a sphincter-saving operation. Elderly people have weaker anal sphincters than young people and therefore old age (>70) speaks against a sphincter-saving procedure. Whether objective assessment of anal sphincter function can be used to predict the outcome of a sphincter-saving operation as regards continence has not been settled. However, it appears reasonable to assume that a patient with a low anal pressure, although without a history of imperfect continence, carries a higher risk of developing incontinence than a patient with normal pressure, and in our experience recto-anal manometry is a valuable tool in selecting the patients most suitable for a restorative operation and to evaluate the mechanisms behind post-operative disturbances.

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Abdominoperineal Resection

Petr Tsarkov

History

In 1908, investigating the pathogenesis of rectal cancer, Miles established the role of the lymphatic system in the spread of malignancy and emphasised the need for synchronous removal of the rectum and its "lymphatic drainage" with the abdominoperineal approach [1].

This event was supposed to be the beginning of state-of-the-art surgery of rectal cancer, though during the following 30 years the Miles operation played an insignificant role in the treatment of rectal adenocarcinomas because of high operative mortality caused by imperfection of anaesthesia technique and peri-operative care [2]. Progress in medicine resulted in a decrease in post-operative deaths and allowed abdominoperineal resection (APR) to yield better long-term results as compared to trans-sacral procedures. Soon APR became the gold standard of treatment of rectal cancer [3].

Further investigation into the principles of spread of rectal adenocarcinomas [4] along with the wide use of stapler techniques and hand-suture colo-anal anastomosis made it possible to largely replace the operation that was "ideal" in the recent past. At the present time, APR is undeniably utilised for adenocarcinoma of the lower third of the rectum, located in close proximity to the dentate line, which can also be involved in malignancy. The use of total mesorectal excision (TME) has enabled surgeons to substantially decrease local recurrence and to increase the five-year survival after APR, though the results obtained for the lower third of the rectum are still worse than those obtained for the middle and upper thirds [5]. The development of a nerve-sparing technique has brought about the improvement in urinary and sexual function outcomes of APR [6]. Nevertheless, the main drawback, abdominal colostomy, has not been eliminated. All the circumstances mentioned have determined the place of APR in the surgery of rectal cancer in the beginning of the 21st century.

Anatomic Background

Prior to considering the indications for APR, it is necessary to describe the specific features of spread of adenocarcinoma of the low rectum. During the last century, there has been the following dominant concept: when the tumour is located to within 5.0 cm of the anal verge, all the elements of anal canal, the ischiorectal tissue and the perianal skin should be removed [7]. In order to evaluate how often the mentioned anatomic structures are involved in malignancy and in which cases it is possible to save them, we have performed a morphological investigation.

Morphological Investigation

Material

Seventy-one specimens were selected to perform a morphological investigation. They represented rectums with adenocarcinoma and contiguous anatomic structures (pararectal and ischiorectal tissues, external and internal sphincters, and perianal skin) obtained as a result of curative APR. In these series of specimens, the lower margin of the tumour was located within 5 cm of the level of perianal skin. Specimens obtained in the course of palliative APR of the rectum or with positive lateral margin were not analysed. All the tumours possessed adenocarcinomas that differed in the degree of differentiation. A high degree of differentiation was characteristic for 19 (26.8%) adenocarcinomas, 44 (62.0%) adenocarcinomas had a good degree of differentiation, whereas a low degree was characteristic for 8 (11.2%) adenocarcinomas. The T2 stage was revealed in 15 observations, T3 in 53 specimens and T4 in three cases. Thus, 68 (95.8%) of 71 tumours examined did not exceed the visceral fascia of the rectum. In three patients only (4.2%) were the contiguous organs involved in malignancy: vagina (1.4%) and prostate (2.8%). The margin of resection of invaded organ remained intact

in all three cases. In 30 (42.3%) cases, the tumours had demonstrated involvement of the upward lymph nodes. In 41 (57.3%) cases metastases to regional lymphatic nodes were not observed. Most of the tumours had a near-spherical shape. The mean values of their longitudinal and transverse dimensions were as follows: 50.5 (35–65)×49 (25–80) mm.

Methods

The macrospecimen was cut through all the layers of rectum by a plane of minimum cancer lesion. After fixing in formalin solution (10%) for 24 h, the specimen was sliced through the tumour by the longitudinal plane at a step of 3 mm.

In order to perform histologic investigation, we selected the sections with the maximum depth of cancer invasion and the lowest distal verge of the cancer. The pectinate area including tumour was subjected to pathomorphometry. The following parameters were measured and summarised in the morphological map: the maximum depth of invasion in the lateral direction, the level of the distal margin of the tumour from the dentate line and perianal skin, the number of lymphatic nodes and their location. The histologic structure (haematoxylin–eosin) and the distal intramural spread of malignancy were studied.

Results

It is worth noting that the cancer invasion decreased gradually in depth outward from the centre of the tumour. The level of maximum invasion therewith was located well above the distal verge of the cancer, on the average, 28.8 mm (5–50 mm) from the dentate line. In the area of distal margin of the tumour, invasion of the cancer into the rectal wall was minimum (Fig. 1). As a rule, the invasion was confined by the mucous and submucous layers of the rectal wall, which is undoubtedly favourable from the viewpoint of implementation of sphincter-saving technique.

When investigating the spread of adenocarcinoma in the circular direction, we noticed that the mean distance from the lateral margin of the cancer to the circular line of resection at a level of maximum invasion was 5 mm (range 1–10 mm). Close examination revealed no cancer cells in the circular margin of resection.

Depending on the location of the lower margin of the tumour from the dentate line, all the specimens were divided into three groups. The first group comprised 18 specimens in which the distal verge of the tumour was located 1–2 cm above the dentate line. The second group consisted of 45 specimens, in which the caudal margin of the tumour was located within 1 cm above the dentate line. The third group comprised 8 specimens in which the tumour involved the dentate line and anal canal to within 1 cm below the anorectal junction.

In the first group, all 18 tumours were presented to adenocarcinomas in T3 stage. Most of them had histologic structure with high and good degrees of differentiation (n=17). Low differentiation was observed in one case. Examination revealed no involvement of the structures of the anal canal, the ischiorectal tissue or the perianal skin. Distal intramural spread of malignancy was not observed in this series.

In the second group, most of the tumours were attributed to adenocarcinomas of high and good degree of differentiation (n=41). A low degree of differentiation was observed in four cases. T3 stage was found in 44 cases and T4 in one case. In 36 of 45 observations the structures of anal sphincter, the ischiorectal tissue and the perianal skin were not involved in malignancy. In eight cases the involvement of the internal sphincter was observed. In this connection, the levator ani muscles, external sphincter, ischiorectal tissue and perianal skin remained intact. Interestingly, in this series, the tumour had a structure of poorly differentiated adenocarcinoma in three of eight cases.

There was only one case of poorly differentiated tumour infiltration of the levator ani muscles, the internal sphincter and the prostate. In this examination, we observed the effect of distal intramural spread of malignancy along the submucous layer and the internal sphincter over a length of 12 mm from the macroscopically determined lower margin of the

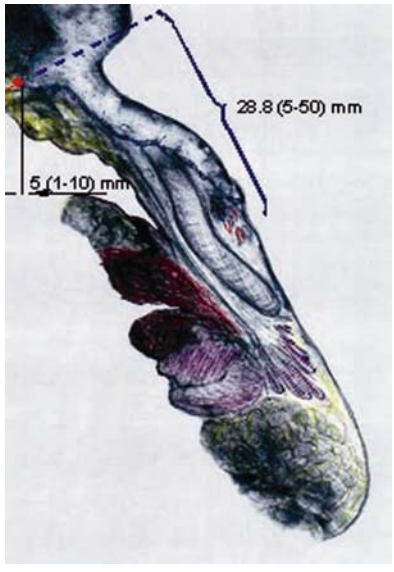

Fig. 1. Level of maximum invasion

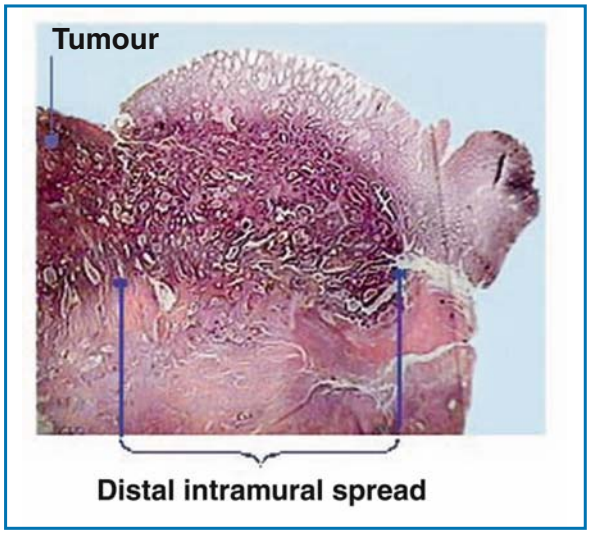

Fig. 2. Distal intramural spread

tumour (Fig. 2). However, the structures of external sphincter, ischiorectal tissue and perianal skin remained intact.

Moreover, in all cases of cancer invasion into the internal sphincter, with the exception of one case with the distal intramural spread of malignancy, the lesion was not total. It was located within the upper third of internal sphincter.

In five of the eight observations in the third group, the tumours were attributed to high and well differentiated adenocarcinomas. The T3 stage was observed in six cases and the T4 in two cases. In all specimens the structures of anal canal were involved in malignancy. In six cases there was involvement of the internal sphincter within its proximal portion. The levator ani muscles, the external sphincter, the ischiorectal tissue and the perianal skin remained intact. Interestingly, in this series, the tumour had a structure of poorly differentiated adenocarcinoma in one of the six cases. In one case only, the complex lesion of the internal and portions of external sphincter were observed. The tumour possessed a low degree of differentiation. In this case, the ischiorectal tissue, subcutaneous part of external sphincter and perianal skin were not involved in malignancy.

One more examination revealed the complex lesion of the levator ani muscles, internal and external sphincter. The tumour also possessed a low degree of differentiation. However, the ischiorectal tissue and perianal skin remained intact. The data obtained in the course of investigation into involvement of the structures of the anorectal area in malignancy are presented in Fig. 3.

It must be emphasised that, in all cases, the perianal skin, subcutaneous portion of external sphincter and ischiorectal tissue remained intact. The puborectal muscle and levator ani muscles were not involved in malignancy in the majority of cases (97.2%). Their lesion was revealed in case of a low degree of differentiation of the tumour only. In every fifth observation, the upper third of internal sphincter was involved in malignancy. However, the incidence of its total lesion did not exceed 3%. The low degree of differentiation was observed in all cases of total lesion of internal sphincter as well as in the presence of distal intramural spread of adenocarcinoma along the submucous layer.

Thus, when the lower margin of the tumour was located within 2 cm above the dentate line, the internal sphincter was rarely involved in malignancy (9/63, 14.3%). In these cases, the tumour invaded its proximal third and the spread into external sphincter (in this case, into levator ani muscles) was revealed in one specimen with a low degree of differentiation of malignancy (1.6%). Other structures of dentate area remained intact.

When the distal margin of the tumour was located below the dentate line, the internal sphincter was invaded in 100% of cases and the external sphincter in every fourth case. Such behaviour can be explained in terms of low degree of tumour differentiation. However, the ischiorectal tissue, subcutaneous portion of external sphincter and perianal skin remained intact even for this group of specimens.

The revealed behaviour of malignancy in the distal area of the rectum can be elucidated as follows: the

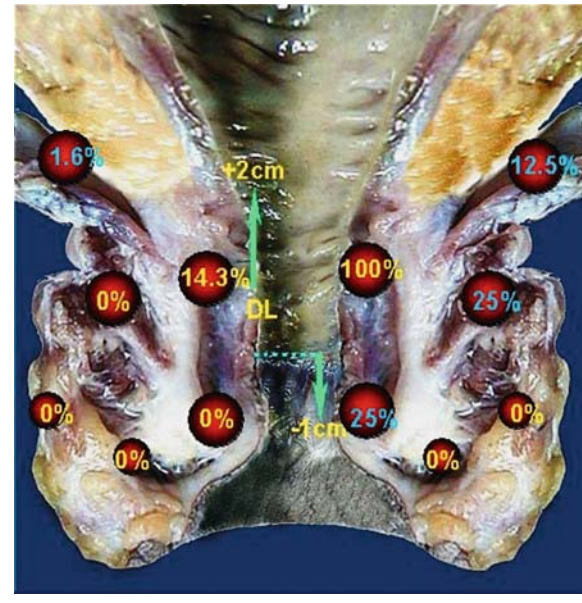

Fig. 3. Incidence involvement of the structures of the anorectal area

anorectal area, once being an integral anatomic–functional formation, is not the same from the viewpoint of its histogenesis. From the viewpoint of providing adequate circular margin of resection, the implementation of TME in the course of the abdominal phase of the operation allows surgeons, along with the removal of the rectum within of the visceral fascia, to take in the specimen the regional lymphatic nodes as well. The inclusion of the longitudinal muscle of anal canal in resection plan makes it possible to provide lateral clearance in the distal area of the specimen with entire or partial saving of anal sphincter.

The data obtained suggest that APR should be undoubtedly utilised when the dentate line and/or parietal fascia of the pelvis are invaded. However, the low differentiated adenocarcinomas can serve as a reason to reject the decision to save sphincter in favour of APR in cases of tumour location within 1–2 cm above dentate line as well.

Indications for APR

The results of morphological investigation currently testify in favour of surgery of low rectum cancer, if only APR and colostomy are to be used, for no more than 20% of such cases, thus for about 6–8% of all patients suffering from rectal cancer. In fact, even in specialised centres, the number of such procedures rises only to 20–30% of those performed for adenocarcinoma of the rectum. This is associated with the fact that the surgeon rejecting sphincter-saving operation in favour of APR should take into account a variety of variables, characteristic for the tumour and the patient.

Tumour Variables

APR of the rectum is conventionally performed when the tumour is located 0–5 cm from the perianal skin. However, APR (with permanent stoma) is not always the appropriate operation. In this case, when a low-dimensional tumour (less than 2 cm in diameter) is characterised by a high or good degree of differentiation, its invasion does not exceed the submucous layer, and the surgeons have no information on whether there is lymphovenous invasion, it is reasonable to apply various local procedures (transanal excision, TEM, diathermocoagulation via anoscope, etc.). At the same time, the T2 or T3 tumours without involvement of internal sphincter and longitudinal muscle in case of highly and well differentiated adenocarcinomas located 1–2 cm from the dentate line cannot be considered as an implicit indication for APR. Such tumours should be judged from the viewpoint of the possibility of implementing resection of the rectum with subsequent formation of either ultralow stapled colorectal or hand-sutured colo-anal anastomosis. Therefore, the surgeon should make the final decision of operative technique upon completion of TME, being certain of the absence of macro- and microscopic symptoms of cancer invasion in the circular and distal margin of expected resection ("rectum neck" in the area of junction to levator). An impossibility of providing an uninvaded margin of any of the lines of resection can serve as an indication to perform APR. Invasion of dentate line or a free margin less than 1 cm is an indication for APR. However, there have recently been discussions of the possibility of using the intersphincteric or "close-shaved" approach to treat such patients when a portion or the whole of internal sphincter is resected [8–10]. Control over continence after such operations is accomplished by the residual portion of anal sphincter in combination with the reservoir technique. It is undeniable that cancer of the low rectum (prevailing situation) can serve as an indication for APR when the parietal fascia are involved as well as when there are symptoms of lymphatic spread (finger investigation, TRUS, MRT), regardless of the distal margin of the tumour from the dentate line.

Patient Variables

The variety of factors which can affect the surgeon's decision whether to perform resection of the rectum should include the condition of anal sphincter, bowel function, patient's age, concomitant diseases and capability of self-care of stoma. Thus, in case of anal incontinence, for patients with adenocarcinoma located 1–2 cm from the dentate line, it is unreasonable to aim for intestine continuity, because incontinence can even deteriorate. Such an approach can be applied to patients with intestine function characterised by urgent desires and diarrhoea. At the same time, upon solving question in favour of APR for patients suffering from the blindness, severe arthritis, mental insanity or neurologic diseases (para- and tetraplegia), intimate conversations with the patients and families caring for them are required because, besides medical indications for colostomy, the social indications play a significant role. One more factor capable of changing the plan of operation from sphincter-saving to APR is a "difficult" pelvis. In this case, not only the general surgeon, but the experienced colorectal specialist faces insurmountable technical obstacles when dealing with the fat and tall male with a narrow, long pelvis.

Operative Technique

APR should start with a discussion with the patient in the course of which he must be informed of the nature of disease, the need of removal of the rectum and anal sphincter and, if required, the need of resection of vagina wall, adnexa or bladder as well as about the formation of colostomy. Prior to the operation, the patient should be examined by a stomatherapist, which along with the selection of a location for a future stoma must as much as possible adapt the patient to the idea of the possibility of living under modified conditions.

Moreover, it is necessary to perform bowel preparation by means of antegrade lavage with 4 l of polyethylene glycol pre-operatively. Until now, the idea of antibacterial preparation of the bowel before operation has not been totally supported.

The two-team approach to APR is preferred. However, the presence of an experienced surgeon-assistant capable of performing the perineal phase of the surgery is an obligatory condition. This will significantly reduce the operative time, enabling surgeons to correct the direction of extraction of the rectum (especially in case of advanced tumours), and facilitate providing the final haemostasis after removal of the specimen. The abdominal team should play the crucial role in extraction of the rectum. In order to proceed with the perineal phase of the operation, it is necessary to complete TME. This is due to the fact that procedures carried out by the perineal team necessarily result in the drift of the rectum in the pelvis area, which prevents the precise extraction of the rectum and the synchronous saving of the autonomic nerves of the pelvis. Moreover, the visceral fascia can be injured. After the TME technique has been developed, the technical difficulties of extraction of the anterior wall of the rectum from the perineal side appear easily surmountable.

After total anaesthesia in combination with a peridural anaesthesia, the patient is placed on the table in a perineolithotomy position. Pneumatic compression devices are fitted to the legs to prevent thromboembolic complications. The perineum of the patient must project over the end of the table. The catheter is inserted into the bladder. Along with urine drainage, this allows attainment of required orientation when the front wall of the rectum in males is extracted. Proctoscopy examination is performed to reassess the rectal cancer and irrigate the rectum until clear. The abdominal and perineum skin (including vagina in females) are prepared in the conventional way.

Abdominal Phase

Incision and Exploration

The midline incision of abdomen is optimal for APR. After examination of abdominal cavity and making a decision to perform the operation, the required exposure is attained with the use of retractors.

Sigmoid Mobilisation

The sigmoid is mobilised by retracting it anteromedially. The incision is extended along the peritoneum at the left of the base of mesentery of sigmoid towards the splenic flexure and caudal to the cul-de-sac. Next the left ureter is retracted down and laterally out of the dissection field. Such an incision is extended at the right of the base of sigmoid. As a rule, the right ureter remains under the peritoneum laterally out of incision.

Ligation of Vascular Pedicle

The mobilised sigmoid colon is retracted anteriorly and laterally. The vascular pedicle is divided from the fascia covering aorta. In this connection, it is necessary to identify superior hypogastric plexus and leave it on the fascia. Upon division of the vascular pedicle up to the area where the a. mesenteric inferior (IMA) takes off the aorta, surgeons should be very careful with the left branch of sympathetic pre-aortic trunk, as the pedicle is closely adjoined to it over a length of 2–3 cm. After confirming that the left ureter is out of the operative field, a high ligation of IMA is performed at the area where it takes off the aorta. When there are no data on the lymphovenous invasion and the tumour is low-dimensional, it is possible to perform low ligation of the vessel just distal to the take-off of the left colic artery. The v. mesenteric inferior is ligated separately according to the level of artery ligation. Next the mesentery of sigmoid is serially clamped, divided and ligated from the point of the pedicle ligation to the level at which the colon will ultimately be divided. This level is determined by holding the colon up to the abdominal wall to be certain the colostomy can be constructed without tension.

Division of Colon and Colostomy Construction

The implementation of this stage prior to rectal mobilisation decreases the probability of contamination, simplifies access to the rectum, provides optimum conditions for stoma construction and prevents paracolostomy complications. Adequacy of the blood supply to the proposed site of division of the colon is assessed. In order to prevent contamination, the colon is divided with the use of GIA in the plane of sigmoid-descending colon junction. The abdominal surgeon clamps the peritoneum of the lateral abdominal wall in the area of the upper edge of the incision at the left of sigmoid. Then the peritoneum is separated from the posterior and lateral abdominal walls up to the plane of the proposed place of stoma construction. A circular portion of skin and subcutaneous fat, 2.5–3.0 cm in diameter depending on the colon thickness, is excised with the electrocautery down to the fascia of abdominal rectus. If excess fat is excised, the stoma may "settle" and the skin edges will be somewhat concave. A cruciate incision is made in the anterior fascia of the rectus and the muscle fibres are separated longitudinally. The posterior leaf of the rectus fascia is incised in a circular manner, so the abdominal wall defect will accommodate entirely to the circumference of the colon. Usually, two fingers properly fit this defect. Next the colon is fed through the extraperitoneal canal and the abdominal wall defect with care taken to avoid a twist in the colon or mesentery. It is ideal to have the colon protruding about 2.0 cm above the skin level. This method of stoma construction provides the absence of lateral paracolostomy space. Therefore, there is no need to place suture on it.

Rectal Mobilisation

Rectal mobilisation is begun posteriorly by lifting the sigmoid up and forward to expose the avascular space in the posterior midline surface filled with areolar tissue. However, the entrance to the avascular space is closed by the right and especially left branches of hypogastric nerve. Therefore, first it is necessary to separate both branches of hypogastric nerve from the visceral fascia. Electrocautery is used to develop the posterior avascular dissection plane staying anterior to the presacral fascia, sacral nerve plexus and median sacral vessels but posterior to the superior rectal artery and mesorectum up to S4 level from which the rectosacral fascia emerges. This fascia, determined as an area where the presacral fascia gives way to fascia propria of the rectum, is incised anterior to the coccyx. Mobilisation is completed at the level of lig. anococcigeum.

Anterior mobilisation is begun by continuing the previously made parallel incisions of peritoneum to meet in the midline at the deepest portion of rectovesical/rectovaginal pouch. In females, a relatively avascular plane along the rectovaginal septum is developed by electrocautery dissection under direct vision. In males, the plane posterior to Denonvillier's fascia and anterior to the rectum is developed by electrocautery dissection distally to the inferior margin of the prostate. Care is taken to avoid injury to the posterior wall of the bladder, seminal vesicles and prostate gland to avoid pelvic plexus injury. If removing the tumour localised at the anterior rectal wall, the approach is altered to include a posterior vaginal wall in women and possibly to include a portion or the whole of the prostate in men if direct invasion into contiguous structures is present.

The final step in rectal mobilisation is to complete the division of the so-called "lateral ligament". The "lateral ligament" on each side is exposed by holding the lateral surface of the rectum in the hand and retracting it to the opposite side of the pelvis. This technique enables surgeons to expose the place of intimate junction of pelvic plexus with the visceral fascia of the rectum. The intimate junction of these anatomic structures is provided by the nerves connecting the pelvic plexus with the rectum and by the branches of the median rectal artery passing through the plexus to the rectum. The performed anatomic investigations have demonstrated that the pronounced trunk of the median rectal artery is observed in 25% of cases [11]. This allows retraction of the lateral wall of the rectum with the use of scissors by coagulation of the branches and even the non-pronounced trunk of median rectal artery. The division and ligation of the tissues by clamps is allowed as a last resort when the trunk of artery is pronounced, because, in such a situation, the pelvic plexus can be injured. Injury of pelvic plexus leads to the urogenital complications. If implementation of APR is required and the two-team approach can be utilised, the perineal team joins the operation.

Perineal Phase

The oncological efficiency of the perineal phase of the operation and its safety directly depend on the professional skills of the surgeon performing it. Thus, this factor must play an important role when assembling the team of surgeons. Usually, the proper position of the patient on the table ensures good exposure from the perineal side. However, if heavy buttocks or a deep anal canal make visualisation difficult, one can suture the buttocks laterally. The per-

ineal operator should first irrigate the now mobilised rectum until clear from secretions, blood and loose bits of tumour. Next the perineal is reprepped and the anal canal pursestring suture of heavy silk is placed and tied.

Incision

An elliptical incision is made with cutting cautery. The incision extends anteriorly from the mid-portion of the perineal body in males or the posterior area of the vagina in females to the plane of coccyx tip. Such an incision is made in a conventional situation. If resection of the vagina is planned, the elliptical incision is extended anteriorly to incorporate the posterior area of vagina. The initial incision is deepened down through the fat of both ischiorectal fossae to the level of the levator ani muscles laterally. The inferior rectal vessels can be controlled by coagulation or suture ligation. Self-retaining or rake retractors facilitate the exposure.

Posterior Dissection

The anococcygeal ligament is divided at the tip of the coccyx to enter the superficial post-anal space. The abdominal operator can retract the rectum anteriorly and guide the perineal surgeon into the correct dissection plane by palpation. This avoids the mistake of lifting the presacral fascia from the bone surface, which can result in the disruption of the presacral venous plexus.

Lateral Dissection

The index finger is inserted through the posterior defect up into the pelvis and then hooks the levator ani muscles laterally. Opposing traction of the rectum tenses the levators, which are serially clamped, divided and suture ligated with an absorbable stitch. The ischial spine defines the extent of lateral dissection.

Anterior Dissection

The skin clamps are pulled anteriorly and the anterior perineal incision is developed in the anterior decussating fibres of the external sphincter down to the superficial and deep transverse perineal muscles. The abdominal operator passes the umbilical tape tied to the proximal rectosigmoid through the posterior dissection plane to the perineal operator who pulls the mobilised rectum and uses it for counter traction to facilitate the remainder of anterior dissection. The transverse perineal muscles are retracted anteriorly. The abdominal operator protects the prostate, seminal vesicles and urethra while the perineal surgeon follows the median raphe and puborectal muscle. Remaining tissues are divided with electrocautery with attention directed to avoid injury to the prostatic capsule or urethra, which is defined by the palpable bladder catheter. The specimen is thus resected *en bloc*. Any bleeding points are ligated or cauterised.

Wound Closure

The pelvic perineal space is irrigated from above and the perineal wound is then closed in layers from below with absorbable sutures. If a posterior vaginectomy has been performed, 2-0 absorbable synthetic sutures placed through the full-thickness of the vaginal wall starting at the apex will be used to reconstruct the vagina. The vaginal introitus is reconstructed before completion of closure of the perineal wound.

Abdominal Closure

In case of synchronous APR, the abdominal operator assists the perineal surgeon to complete resection. After irrigation of abdomen and pelvis cavity and completion of haemostasis, a soft drain is placed through a lower abdominal wall. As a preventive measure for ileus, the integrity of pelvic peritoneum is reconstructed. Fascia and skin are closed in a routine manner.

Maturation of Colostomy

Eight or ten absorbable sutures are placed around the circumference of the stoma between the skin and the seromuscular layer of the bowel without full-thickness bite of the colon at the edge of the stoma. The area of sigmoid with stapler suture is excised so that an excess of about 2 cm protrudes above the skin. The midline wound is dressed with an aseptic bandage.

Post-Operative Care

The enterostomal feeding is begun within two days of APR. Anti-embolism prophylaxis with anticoagulants and pneumatic compression stockings (elastic

bandaging of legs) is continued for seven days after the operation. The drain inserted into the pelvis cavity is removed as soon as drainage is <30–50 ml per day. The bladder catheter is usually removed within three days of surgery. Enterostomal therapy nurses begin teaching the patient and his family appropriate care of the colostomy and help alleviate anxiety by answering all their questions. In our series, the post-operative stay after APR averages 8–10 days.

Clinical Results: Post-Operative Complications and Mortality

One hundred and fifteen patients who had undergone curative APR from 1999 to 2004 at the Moscow State Scientific Center of Coloproctology were reviewed retrospectively. All these procedures were performed for the treatment of adenocarcinoma of the rectum. The series comprised 46 males and 69 females with an average age of 58.0±9.143 years. No patient had undergone pre-operative radiotherapy. The average duration of the operation was 205.7±42.48 min (min. 120, max. 320 min) with a blood loss of 363.3±284.3 ml (from 150 to 1500 ml). 17.4% percent of patients received a blood transfusion, on average 2 units. Indications for transfusion today have markedly changed and most patients do not require transfusion. The perineal wound was primarily closed and drained in 95.7% of patients. Five (4.3%) patients had the perineal space open.

We had no hospital deaths in this series. Post-operative mortality has remained relatively stable over the past two decades and varied from 0 to 4%. The majority of operative mortality in reported series are related with cardiorespiratory and septic complications. While mortality is relatively low, morbidity varied from 15 to 35% [12, 13].

In this series, three (2.6%) patients suffered from severe intraoperative complications: ureteral injury, 1 patient; lacerated internal iliac vein, 1 patient; bladder injury, 1 patient; all patients were managed successfully at the same operation. Thirty-four (29.6%) patients developed post-operative complications. Urologic problems constituted the majority of complications.

Specific Complications of APR

Bladder Dysfunction

Urologic problems constitute the most frequent and troublesome complications following APR. Urinary dysfunction was observed in 23 cases. While bladder neck or prostate angulations may be contributory, the majority of micturition disturbances are due to neurologic injury. As voiding dysfunction after APR is common and transitory, one can expect it to subside within three to six months post-operatively.

Fowler and coworkers warned that if large volume retention in the post-operative period secondary to bladder denervation is not recognised and remains untreated, bladder rehabilitation and restoration of normal voiding may be impossible. Many Authors advocate the use of urodynamic studies in order to identify patients at risk of developing urologic problems and to detect early post-operative voiding dysfunction.

Urinary dysfunction was of particular interest in the evaluation of the nerve-preserving procedure effectiveness.

Sexual Dysfunction

Male sexual dysfunction is regulated by the autonomic nervous system via the pelvic plexus which lies posterolateral to the bladder. Sympathetic nerves are responsible for ejaculation, while parasympathetic nerves govern erection. Sexual dysfunction after APR defined by partial or total impotence, loss of emission or retrograde ejaculation was observed in 6/40 (15%) who had normal sexual function prior to operation.

Of the female patients, 83.6% were able to experience arousal with vaginal lubrication and 90.1% could achieve orgasm.

Urinary Tract Infection

Urinary tract infection is a very common sequela to APR. This complication occurs in 6–32% of observations [14]. Contributing factors include the use of universal urinary catheter and urinary stasis.

Perineal Complications

In our series of 115 patients undergoing APR, 6.1% had perineal complications. In one case a perineal hernia was observed. Seven patients had a wound infection with delayed healing and the persistence of chronic perineal sinus. Only two of them required surgical repair.

Stomal Complications

An array of stomal complications can occur in patients undergoing APR. The majority of these are

preventable by careful attention to site selection and operative technique. Stenosis, retraction or prolapse was reported to occur in 8 (6.9%) of 115 patients. The incidence of paracolostomy hernia and prolapse was 5/115 (4.3%).

Most complications can be minimised if APR is performed by an experienced team with knowledge of relevant pelvic anatomy paying careful attention to details of operative techniques.

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Laparoscopic and Robotic Surgery in Rectal Cancer

Annibale D'Annibale, Emilio Morpurgo, Nicola Menin

Introduction

Laparoscopy has been one of the most important innovations in the surgical field in recent years, but its use for the treatment of colorectal malignancies is still controversial due to:

1. early reports of port site implants;
2. concern about performing an oncologically proper resection with adequate margins and lymph node dissection;
3. concern about long-term survival;
4. a steep learning curve.

Port Site Implants

Port site implants were described in the early reports, so it was suggested that laparoscopic colorectal resection only be performed within controlled trials [1]. The reported port site metastases [2] occurred soon after the colorectal resection in patients with large tumours, and when the cancer was heavily manipulated during the procedure, thus suggesting the possibility of neoplastic cell exfoliation during the resection [3]. With growing experience, it is now clear that the incidence of port site metastases is no different from that of wound recurrence after conventional open surgery, as reported by several Authors [4–12]. Nevertheless, adequate manoeuvres are needed to prevent this complication, avoiding tumour manipulation, preventing air leakage through port sites (the so-called chimney effect) and desufflating the abdomen before removing the trocars. The use of proper sleeve wound protection for the mini-laparotomy is also recommended, to avoid contact between the colon and the wound during the exteriorisation of the specimen because cancer implants have been described at the extraction site.

Proper Oncological Resection

It is generally agreed that the definition of proper oncological resection is based on the adequacy of the tumour-free margins, specimen length and number of lymph nodes retrieved. Many reports from uncontrolled and randomised studies show that a proper oncological resection based on these principles can be done laparoscopically, following the principles of surgical oncology [5, 6, 13–15]. Adequate laparoscopic resections have also been described specifically for the rectum and formal total mesorectal excisions can be performed [16–19].

Long-Term Survival

Shorter hospital stays and faster recovery times have been described after laparoscopic colorectal resection [5, 7, 9, 13, 14, 16, 18, 20] and now, with growing experience and longer follow-ups now becoming available, the literature suggests that long-term survival after laparoscopy does not differ from that of open surgery [9, 13, 14, 21]. This has also been demonstrated in randomised studies [9, 14].

Steep Learning Curve

Laparoscopic colorectal resection is a technically demanding procedure with a steep learning curve [22]. New surgical skills need to be learned and many colorectal surgeons do not have such specific training. Laparoscopic instruments are straight, with no articulation at their tips. In addition, the surgeon must learn to operate watching on a two-dimensional monitor. These disadvantages may be overcome, however, by the recent introduction of robotic technology in the operating room (OR). The robotic device is designed to transfer the movements directly from the surgeon's hand to articulated instruments driven by robotic arms and, at the same time, to allow a real three-dimensional view of the surgical field. It has been demonstrated that an equally valid oncological resection and comparable surgical results can be obtained by standard laparoscopy and using the robotic approach [23].

Based on this evidence, it is now clear that the laparoscopic approach can be offered to patients for the treatment of colorectal cancer, providing the procedure is performed by surgeons with plenty of experience in this field.

The laparoscopic technique differs in several ways from the standard open technique. The differences include not only a technically different approach to the colon, but also a different and particular preparation of the patient for surgery, a different position of the patient on the OR table, and a completely different set of equipment. Surgeons willing to perform this type of surgery need to have an in-depth understanding of the technology used in laparoscopy.

Equipment

Laparoscopic Cart

The laparoscopic cart components are:
- a carbon dioxide source and insufflator
- a light source
- a camera system
- video monitors
- recording media.

Carbon dioxide source and insufflator. Carbon dioxide is stored in containers at a pressure of about 50 bar, so the containers must be carefully secured to the cart to prevent accidents in the OR. They are connected to an insufflator, which can generate and control the flow of CO_2 into the abdominal cavity, assuring a maximal flow of 30 l/min. The machine has automatic pressure and flow regulators that adjust the flow of CO_2 to maintain a stable intra-abdominal pressure of 12–14 mmHg. Acoustic and visual alarms can be preset and alert the surgeon in the event of any change in abdominal pressure. Flow per minute, abdominal pressure, gas volume used and insufflation pressure are constantly indicated on the machine.

Light source. The light source is normally a 300-W xenon lamp producing a light very similar to sunlight allowing for automatic or manual light intensity regulation. It has a stand-by position that allows the power of the light to be reduced when it is not needed without turning the lamp off, thereby prolonging lamp life.

Camera system. The camera system is connected to the camera and the 30° laparoscope. It has a video input and three outputs with different resolutions. The red, green and blue (RGB) output is the one with the best resolution power and must be connected to the primary video monitor. Colour must be calibrated by white balancing before starting each procedure. The remaining outputs can be used for a satellite monitor and the recording system.

Video monitors. A high-resolution video monitor is connected to the camera system. It is preferable to connect it using 2 outputs from the camera system (RGG and Y/C) so as to be able to change channel in the event of one of the connections failing. One input to the video should be connected to a video recorder to enable a check on what the video recorder is recording at any given time.

Recording media. Several types of video recorder are available (digital or analogue), so images can be stored in analogue VHS, U-matic or Betacam recorders. It is preferable to use optical recordings that allow for the storage of images in optical disks (DVD, CD).

Traditional laparoscopy significantly differs from open surgery and new, unnatural technical skills have to be learned to perform major operations such as colorectal resections proficiently. In laparoscopy, there is a loss of manual dexterity because: (1) the instruments are straight and have a fulcrum at the port entry, so movements are reversed; (2) straight instruments completely lack the complex articulation characterising a human hand; (3) there is no three-dimensional view as in direct binocular human vision.

A new generation of advanced robotic systems has recently been designed to overcome these drawbacks, however. The da Vinci robotic surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA) offers a three-dimensional view, and it exactly translates the surgeon's hand movements to the tips of the surgical instruments, which have a wrist-like articulation. In addition, it holds the camera in a stable position that can be adjusted directly by the surgeon to optimise the view of the surgical field.

The da Vinci® Robotic Surgical System

The da Vinci robotic surgical system (Intuitive Surgical Inc., Sunnyvale, CA USA) has three components: the vision cart, the master console and the surgical cart.

Vision cart. This component is roughly similar to a standard laparoscopic cart, but with some substantial differences. It holds the dual light source and the image processor for the two cameras that are installed on the single endoscope, which is consequently able to provide a 3D image for the surgeon. It also holds a standard laparoscopic CO_2 insufflator and a standard laparoscopic monitor for the assistants and the scrub technician.

Master console (Fig. 1). This is where the surgeon sits. It contains the computers that process the combined images to create a true 3D image. The surgeon looks down into the viewer as if he were looking straight at the surgical field. He places his hands on

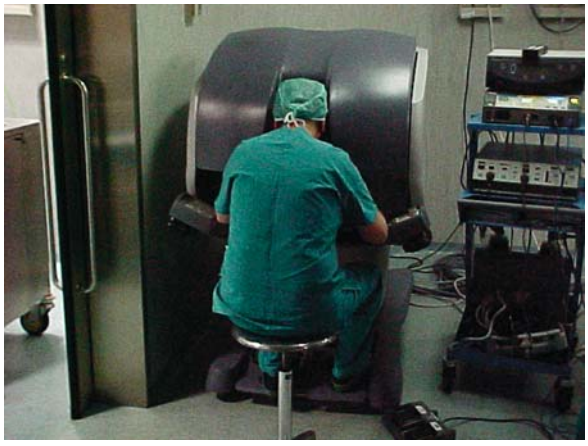


Fig. 1. Robotic console

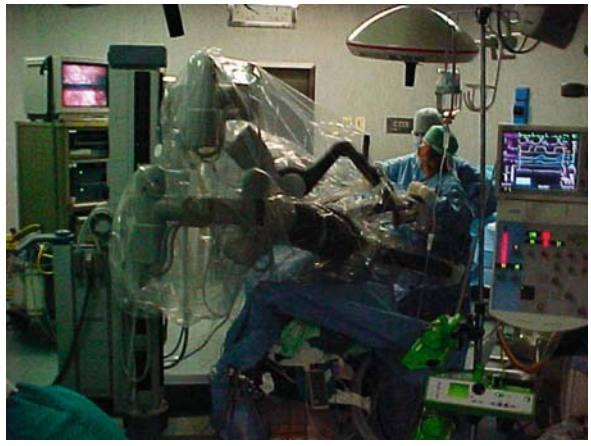


Fig. 2. Robotic arms

the control handles located in the lower part of the console and, by moving the joysticks, he transfers his movements to the robotic arms. Foot pedals at the console provide control for the electrocautery, as well as a clutch.

Surgical cart (Fig. 2). This consists of the 3 robotic arms mounted on a movable chassis. The manipulators (which are covered with sterile drapes during the procedures) are mounted on a central column placed on the wheel-mounted surgical cart. Two arms are for holding the surgical tools and respond to the movements of the surgeon's hands, while one is for holding the three-dimensional stereo-endoscope and camera. The arms have three degrees of freedom (pitch, yaw and insertion) and they hold specifically designed instruments that have a wrist-like movement at their tip.

Patient's Position and Operating Room Setup

The patient lies supine on the OR table, with legs lying flat and initially closed. The terminal part of the OR table must allow for the patient's legs to be opened to perform the anastomosis at the end of the operation. If a Miles procedure or a handsewn, pull-through anastomosis are planned, the legs are subsequently positioned on Allen stirrups, but are initially laid flat to avoid any interference with the surgeon's hands and instruments during the procedure, flexing the legs later, when the perineal part of the operation is over. Both arms are tucked.

During the procedure, patients are placed in a steep Trendelemburg position and rotated to the right, so they must be carefully secured to the bed with bilateral shoulder braces, with one brace positioned on a level with the right deltoid to prevent them from sliding when the table is tilted. Braces are wrapped with gel or foam cushions. To avoid nerve stretching, the position must be checked before anaesthesia is induced, with the patient still cooperative.

Laparoscopy

The surgeon stands at the patient's right side and watches the monitor on the laparoscopic cart, which stands on the opposite side; the assistant stands on the contralateral side, or may move to the right during the procedure to hold the camera more comfortably. The scrub technician stands near the patient's right leg. The remaining devices (bowie and harmonic scalpel carts, suction-irrigation pump) are positioned according to OR custom.

Laparoscopic Instruments

Standard laparotomic instruments must be readily available in case the procedure has to be unexpectedly converted. Specific laparoscopic instruments include graspers, cautery hook, scissors, harmonic scalpel, right angle, staple appliers, laparoscopic linear staplers and circular stapler. Retractors and uterine manipulators may be used, if necessary, during pelvic dissection. The bipolar coagulator has proved very effective in controlling oozing bleeding.

Robotics

The da Vinci robotic system is a heavy, bulky instrument and needs a large OR. The proper positioning of its three components in the room is crucial to minimise the need to move it around the room. As a general rule, the robotic arms are placed on the same

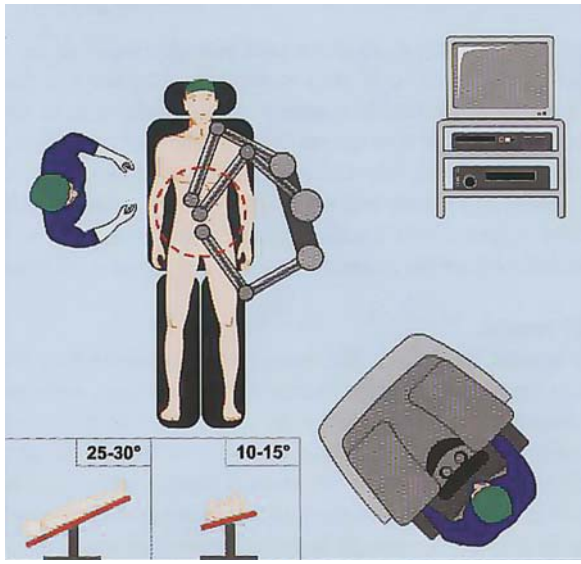


Fig. 3. Position of robotic arms during left colon dissection

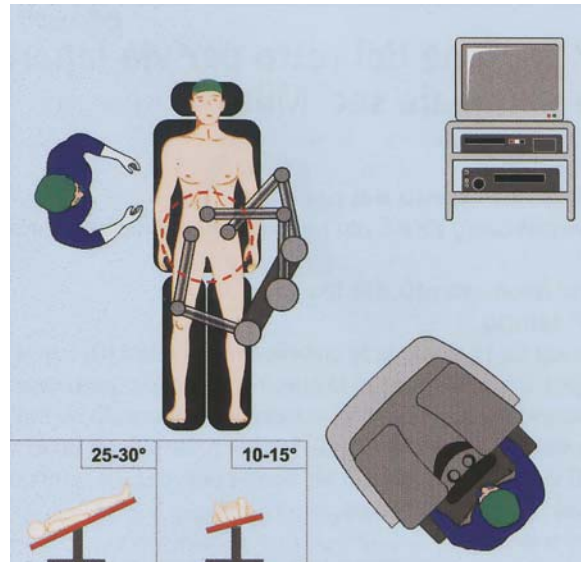


Fig. 4. Position of robotic arms during lower rectum dissection

side of the patient as the lesion (Figs. 3, 4), so for surgery of the left colon and rectum the arms are placed on the patient's left side. The vision cart is positioned at the patient's feet so that the assistant and scrub nurse have an optimal view. The master console is at the patient's side, about 10 feet away to allow enough space for the robotic arms, the scrub nurse and the assistant to move. With the console in this position, the surgeon also has complete visual control of the surgical field and robotic arms. All the instruments are prepared in the room before the patient's arrival. After anaesthesia has been induced the robotic arms are wrapped with sterile plastic sheets and moved up to the operating table. The assistant stands at the patient's right side.

Robotic Instruments

Specifically designed robotic instruments driven by the da Vinci's arms include graspers, a cautery hook, scissors, a needle holder and a harmonic scalpel. The assistant helps the surgeon using standard laparoscopic instruments.

Surgical Technique

Specific Anatomical Considerations

During embryological life the mesentery of the primitive gut is oriented anteriorly. When the bowel re-enters the abdominal cavity, the mesentery of the left colon rotates towards the left and the mesentery containing the vessels fuses with the fascia of Gerota and the retroperitoneum. The plane that originates from this fusion is virtually avascular. This plane must be followed and enables the left colon to be mobilised with its mesentery, vessels and lymph nodes. The inferior mesenteric vein (IMV) can be recognised at Treitz ligament level, where it enters underneath the pancreatic tail (Fig. 5). The inferior mesenteric artery originates from and forms an acute angle with the distal part of the aorta (Fig. 6); it can be recognised by opening the pre-aortic plane, where the mesenteric nervous plexus surrounds the

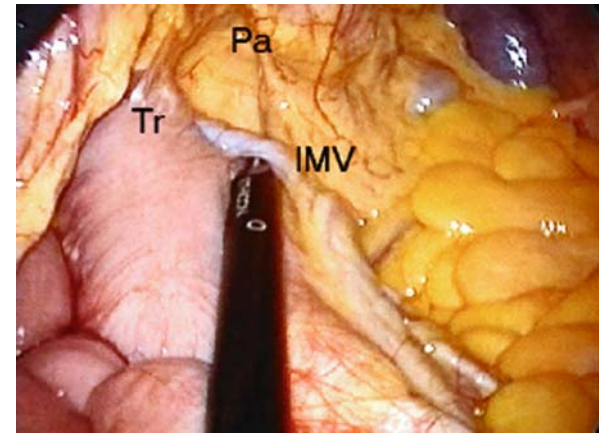


Fig. 5. *Tr*, ligament of Treitz; *IMV*, inferior mesenteric vein; *Pa*, pancreas

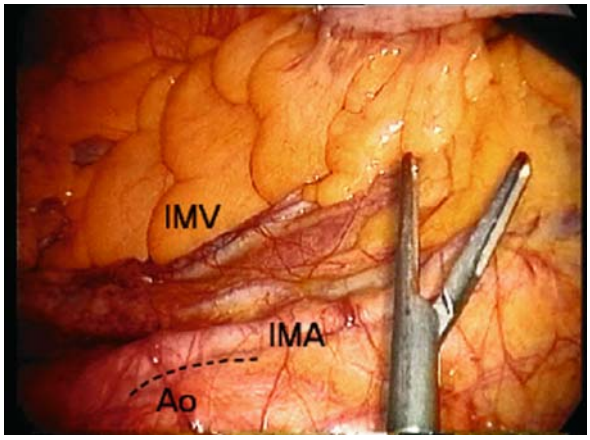


Fig. 6. *Ao*, aorta; *IMA*, inferior mesenteric artery; *IMV*, inferior mesenteric vein. The dotted line indicates the site of peritoneum incision to isolate the artery

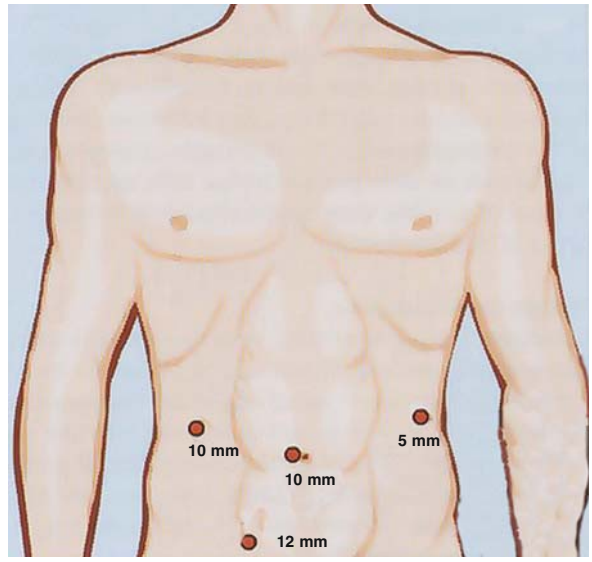


Fig. 7. Position of trocars for laparoscopic rectal cancer surgery

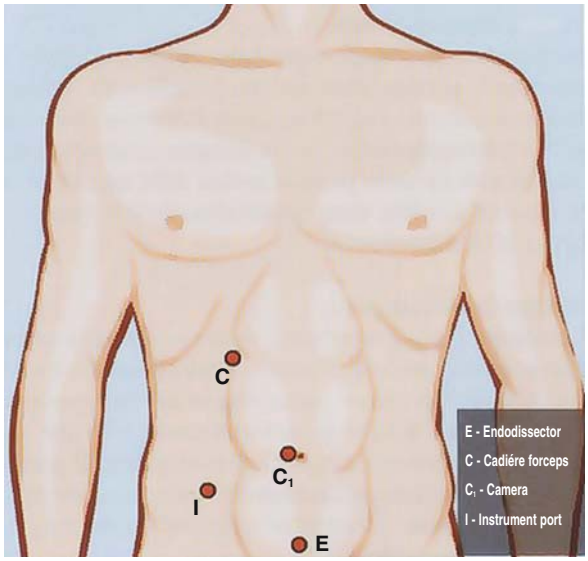


Fig. 8. Position of trocars for left colon dissection during robotic rectal surgery

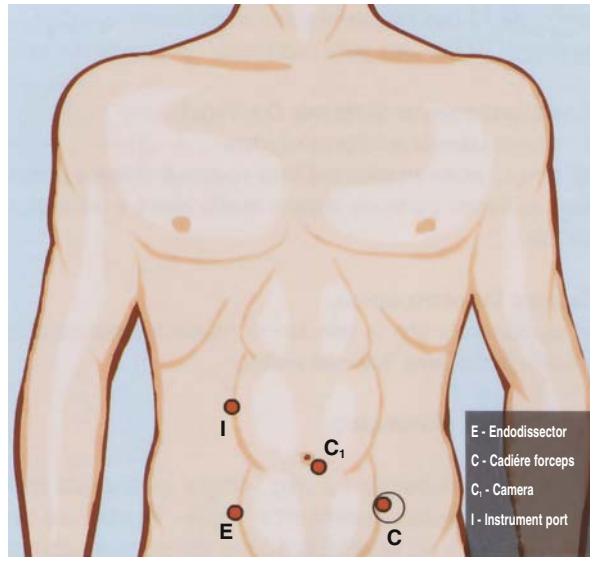
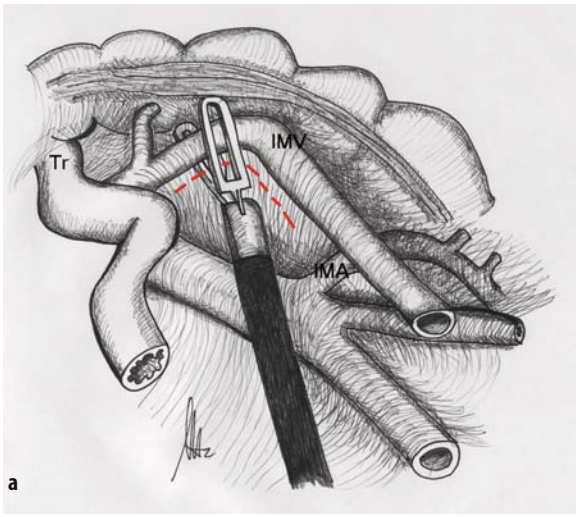


Fig. 9. Position of trocars for robotic dissection of rectum

origin of the inferior mesenteric artery. After vascular ligation, if the avascular plane behind the mesentery of the left colon is followed properly, it leads down to the pelvis into the vascular plane behind the mesorectum, which is mobilised together with the rectum. Here, the hypogastric nerves must be identified and spared.

Port Positioning and Surgical Field Setup

Ports are positioned as shown in Fig. 7 for laparoscopic resections and in Figs. 8 and 9 for robotic resections. The umbilical camera port is created with an open technique and the remaining trocars are positioned under vision after pneumoperitoneum has been created. For laparoscopy, 10-mm ports are used for the camera, the right hypochondrium and



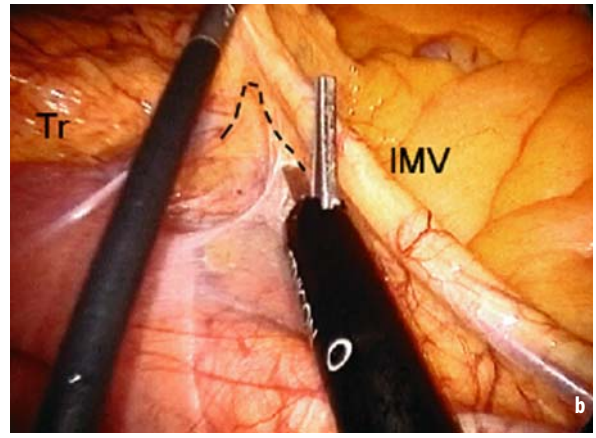


Fig. 10a, b. *Tr*, Treitz; *IMV*, inferior mesenteric vein; *IMA*, inferior mesenteric artery. The IMV is identified at the ligament of Treitz; the peritoneum is opened underneath the vein

the left flank; a 12-mm port is created in the right iliac fossa to allow for the use of the endo-GIA. Robotic ports are 8 mm and the camera port is 12 mm. The robot is first positioned on a level with the left flank, using the trocars in the right iliac fossa and right hypochondrium, and dissection of the left colon is performed. For dissection of the lower rectum, the position of the robot must be changed to left thigh level and works through the 2 ports in the iliac fossae. If a Miles procedure is adopted, the trocar in the left iliac fossa is used for the colostomy. The patient lies in a Trendelemburg position, rotated to the right. The small bowel is pulled out of the pelvis and positioned in the right hypochondrium to expose the ligament of Treitz, with the origin of the IMV.

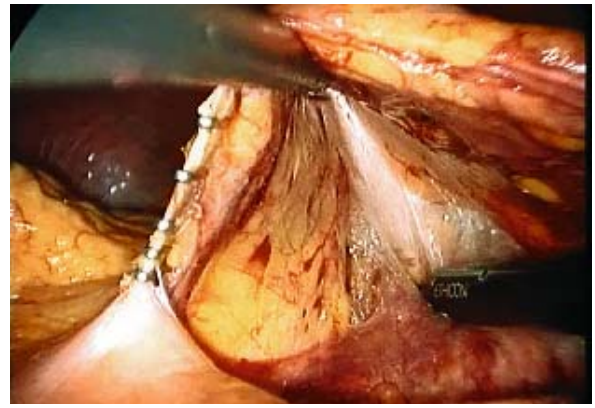


Fig. 11. The mesentery of the left colon is lifted from the fascia of Gerota underneath the inferior mesenteric vein

Identification of the Inferior Mesenteric Vein

The IMV is identified at Treitz ligament level (Fig. 10). To facilitate the identification of the vein, the ligament of Treitz can be pulled carefully to the right. Once the IMV has been identified, the avascular plane between the vein and the fascia of Gerota is opened by sharp dissection and the mesentery of the left colon is detached from the retroperitoneum forming a sort of tent. The vein is clipped but not yet divided because delicate traction on it facilitates the sharp dissection along this plane (Fig. 11).

Identification of the Artery

To enable proper identification of the artery, the Trendelemburg position may be further increased so as to draw the loops of small bowel out of the pelvis. The plane of the right iliac artery is identified and the pre-aortic plane is opened. The IMA is identified and cautiously isolated (Figs. 12, 13). The magnification of the laparoscope enables the identification of the nerve fibres that must be spared posteriorly (Fig. 14). The artery is clipped and divided, and this portion of the mesentery of the left colon is sharply dissected from the retroperitoneum and the ureter is recognised (Fig. 15). This dissection of the mesentery of the left colon from the retroperitoneum must be completed as far as possible in the middle to lateral direction, so that little remains to perform from the left abdominal gutter.

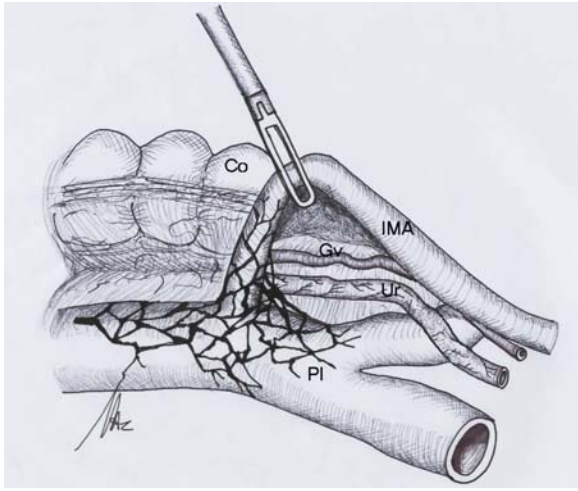


Fig. 12. *Pl*, nervous plexus; *IMA*, inferior mesenteric artery; *Co*, colon; *Gv*, gonadal vessels; *Ur*, ureler. The IMA is identified and the peritoneum is opened just underneath it

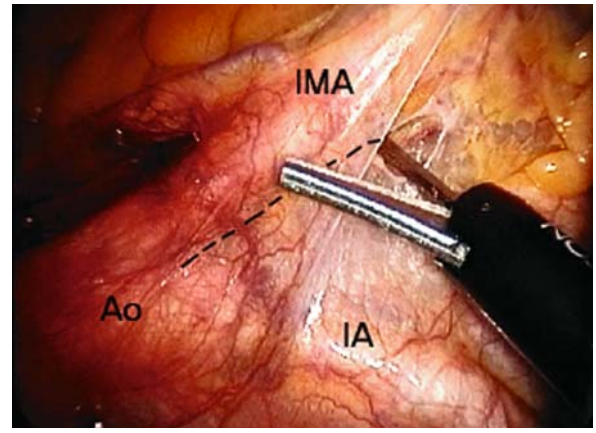


Fig. 13. *IMA*, inferior mesenteric artery; *Ao*, aorta; *IA*, right iliac artery

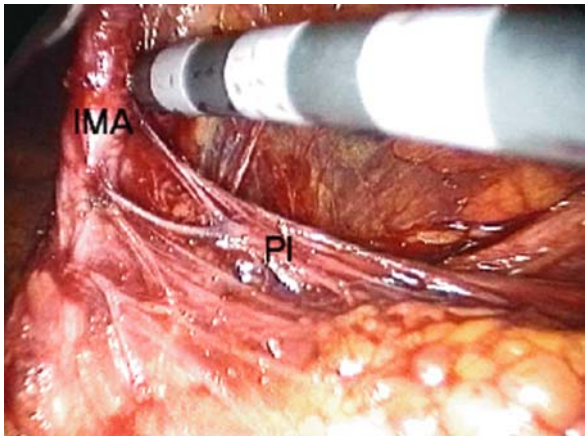


Fig. 14. *IMA*, inferior mesenteric artery; *Pl*, nervous plexus

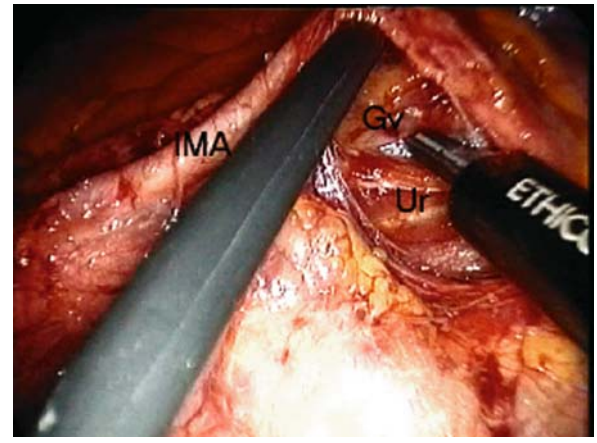


Fig. 15. *IMA*, inferior mesenteric artery; *Ur*, ureter; *Gv*, gonadal vessels

Splenic Flexure Take-Down

A hole is made in the distal part of the mesentery of the transverse colon, above the tail of the pancreas (Figs. 16, 17). This allows a flow of gas into the lesser sac and thus facilitates the separation of the omentum from the colon, which is taken down from the middle third of the transverse colon (Fig. 18). The assistant surgeon helps by pulling the transverse colon towards the pelvis with a grasper introduced in the left flank. The splenic flexure is then carefully detached from the spleen with the harmonic scalpel. If the patient is particularly tall or obese, this operation may be completed using the access in the left flank. At this point, mobilisation of the left colon is completed by detaching the residual peritoneal attachments in the left abdominal gutter.

Isolation of the Rectum and Mesorectum

Following the avascular plane identified after dividing the IMA, the plane between the mesorectum and the presacral fascia is entered. It has a typical cotton candy appearance that indicates the proper plane of dissection (Fig. 19). The dissection is continued down to the plane of the levator ani, sparing the hypogastric nerves, and the typical bilobated appear-

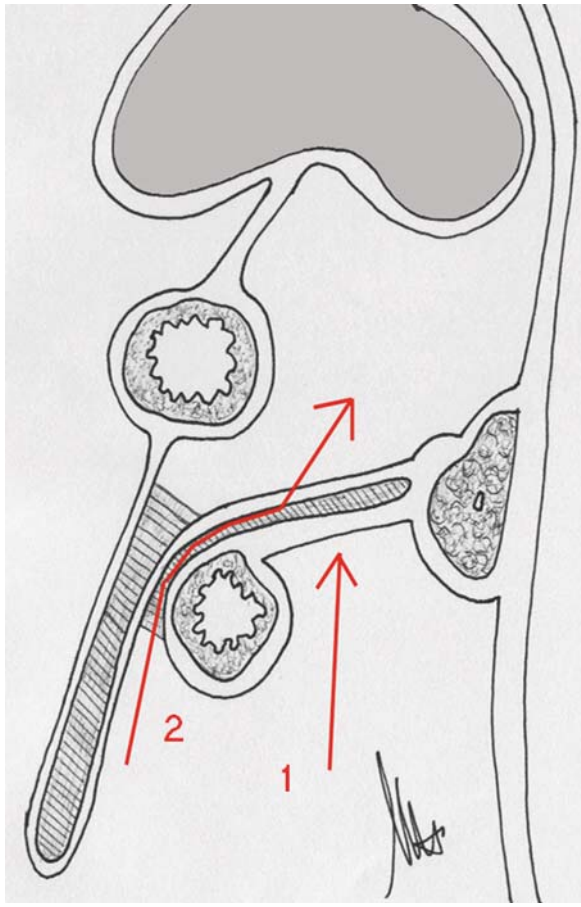


Fig. 16. To take down the splenic flexure, first a hole is made in the mesentery of the distal part of the transverse colon, just above the pancreatic tail (*arrow 1*); then the omentum is separated from the transverse colon (*arrow 2*)

ance of the mesorectum comes into view (Fig. 20). The rectum is isolated by sharp dissection, pushing anteriorly on the rectum. Once the rectum has been isolated posteriorly, the anterior peritoneal reflection is opened and the anterior aspect of the rectum is isolated from the vagina or seminal vesicles and prostate. If the cancer is located in the upper third of the rectum, the mesorectum is divided with the harmonic scalpel below the cancer, and the rectum is stapled with a green endo-GIA (Fig. 21). If the tumour is in the lower two thirds of the rectum, a total mesorectal excision is performed and the rectum is divided just above the dentate line.

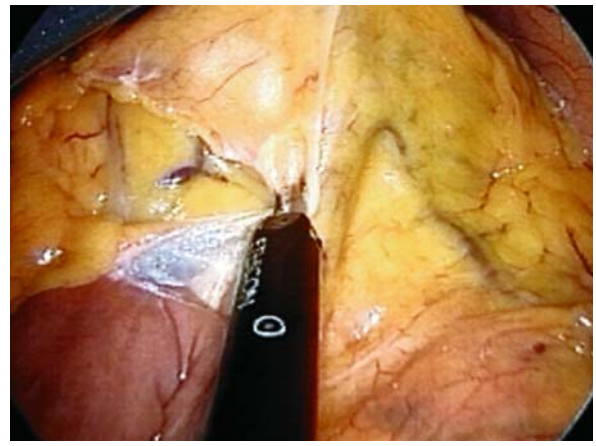


Fig. 17. Hole in the mesentery of the transverse colon

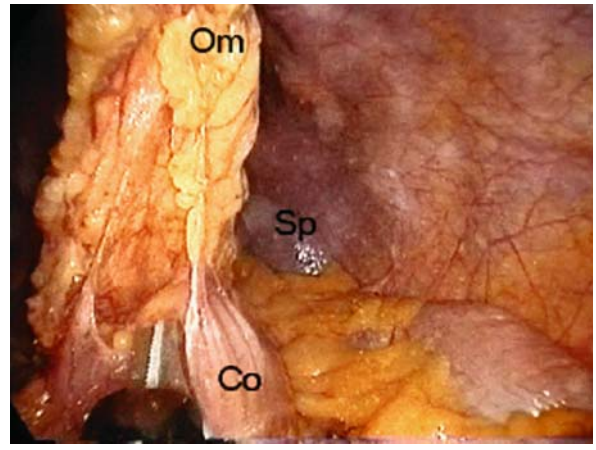


Fig. 18. Take-down of the omentum from the transverse colon. *Om*, omentum; *Co*, colon, *Sp*, spleen

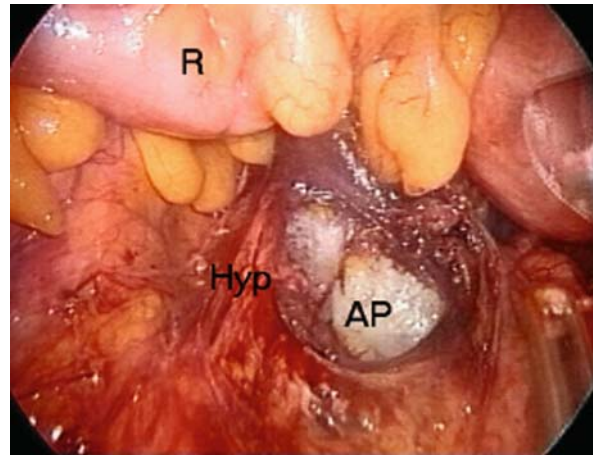


Fig. 19. The cotton candy avascular plane between the rectum and mesorectum and the presacral fascia are identified. *AP*, avascular plane; *R*, rectum; *Hyp*, left hypogastric nerve

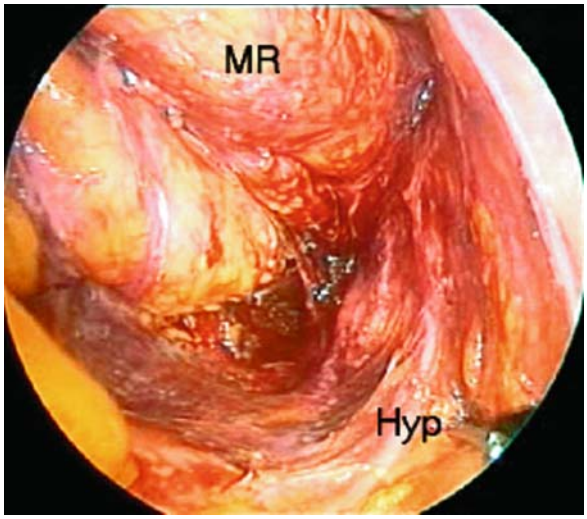


Fig. 20. *MR*, mesorectum; *Hyp*, right hypogastric nerve

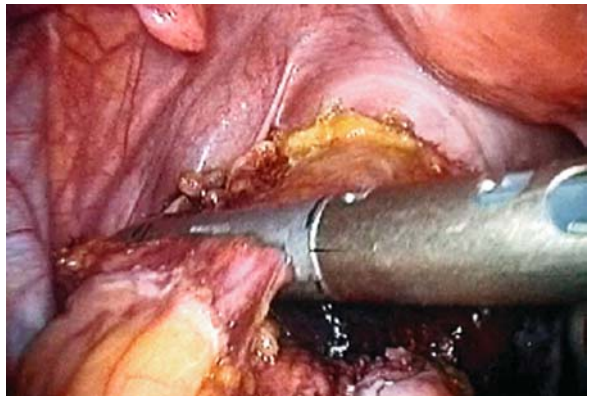


Fig. 21. The rectum is stapled

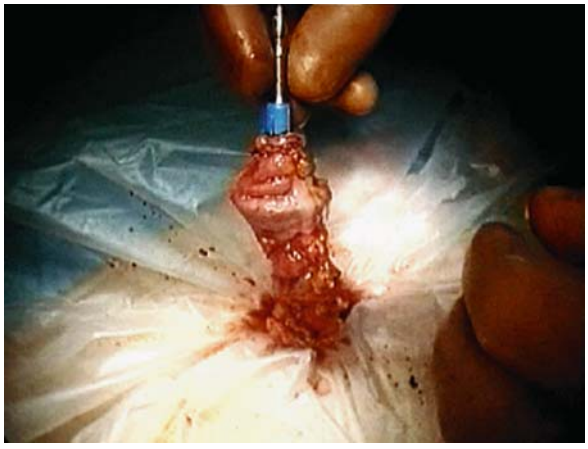


Fig. 22. Exteriorisation of the specimen; the mini-laparotomy is protected

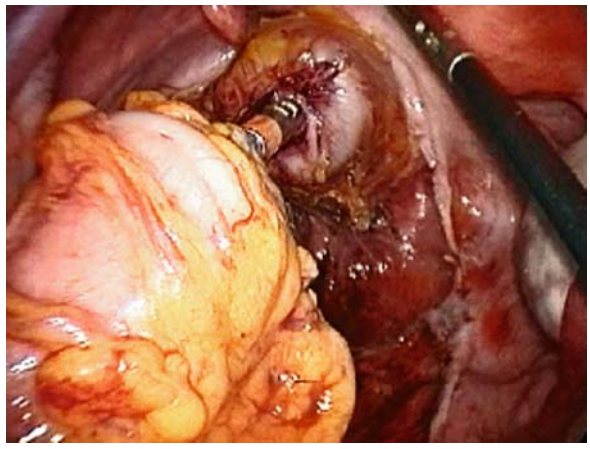


Fig. 23. Anastomosis

Exteriorisation of the Specimen

Once the rectum has been divided, a mini-laparotomy is performed. The mini-laparotomy can be either a Pfannestiel incision or a supra-umbilical midline incision. The Pfannestiel incision has better cosmetic results but cannot be easily extended in case a wider access is needed for some reason, whereas midline laparotomy is very easy to extend, so we recommend the latter for those who are at the beginning of their experience. The laparotomy must be protected to prevent contamination or insemination by neoplastic cells during the extraction of the specimen (Fig. 22). The proximal portion of the colon is resected extracorporeally and the anvil for the circular stapler is positioned. The laparotomy is closed, pneumoperitoneum restored and an end-to-end straight anastomosis is performed (Fig. 23). The anastomotic rings are checked to make sure they are complete through 360°; a pneumatic test is performed, submerging the anastomosis in water and insufflating air through the anus. Two perianastomotic drains are positioned (Fig. 24). Before removing the trocars, it is important to check for bleeding from the insertion sites.

If a handsewn anastomosis is planned, a transanal standard mucosectomy is performed after positioning a Lone Star retractor. The specimen is removed through the minilaparotomy and a pull-through handsewn anastomosis is performed. For Miles procedures, a standard perineal dissection is performed

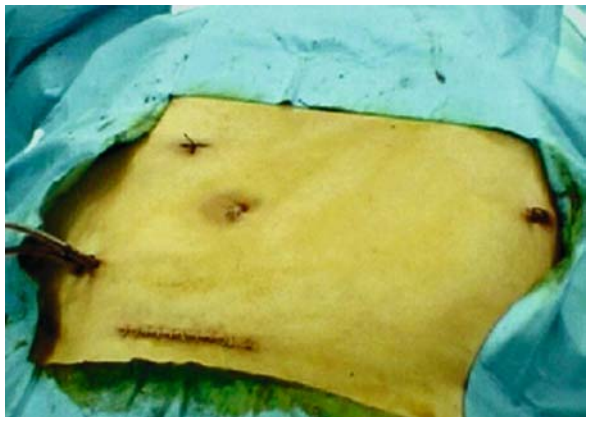


Fig. 24. The abdomen after anterior resection

and the specimen is removed through the colostomy site or through the perineum.

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Total Anorectal Reconstruction with an Artificial Bowel Sphincter

Giovanni Romano, Francesco Bianco, Guido Ciorra

Background

Although, in recent years, the use of mechanical staplers has significantly extended the indications for sphincter-saving operations, abdominoperineal resection (APR) is still an option in the surgical treatment of cancer of the low rectum. In fact, in patients with very low rectal tumours or tumours of the anal canal, rectal resection is the treatment of choice [1, 2]. In these patients a definitive colostomy represents both an anatomical impairment and a psychological handicap, and significantly impairs quality of life (QoL) [3].

The first attempt at perineal colostomy was made in 1930 by Chittenden using a flap of the gluteus maximus as a neo-sphincter [4]. In 1950, Margottini reported a series of 90 patients with a perineal colostomy following resection of the rectum [5]. In 1952 Pickrell reported the results of graciloplasty to treat anal incontinence in children [6]. In 1986 Cavina [7] presented his initial experience of anorectal reconstruction following Miles resection adding electrostimulation (EMS) of the transposed muscle in order to prevent atrophy and improve its performance. In 1989, Williams [8] published the results of his experience with perineal colostomy and graciloplasty following rectal resection, associated with an implantable system. Other experiences of this subject were subsequently reported by Cavina [9–11], Beaten [12] and Williams [13, 14].

The implantation of an artificial bowel sphincter (ABS Acticon ABS – American Medical Systems, Minneapolis, MN, USA) has been carried out in patients with faecal incontinence (FI) [15–19]. We believe this procedure might be useful in patients previously submitted to Miles procedure.

Materials and Methods

Between 1999 and 2003 we carried out a total anorectal reconstruction (TAR) in 12 patients previously operated on with an APR by performing a perineal colostomy and placing an artificial bowel sphincter around the perineal stoma [20, 21]. This procedure was performed by three surgeons in different institutions according to a common protocol. Ten patients had been operated on for rectal cancer, one had had a colostomy in childhood for rectal agenesia and one patient had been treated with a Miles operation 10 years before for a giant benign connectival tumour of the pelvis (Table 1). One patient was male and 11 were female; the mean age was 54 years. The tumour stage in the patients with rectal cancer was T2N0M0 in five patients, T1N0M0 in three patients and T2N0M0 in one patient. All patients were carefully evaluated both psychologically and about their ability to manage the device. The procedure was approved by the local ethics committee. All the patients were informed about this technique and written consent was obtained from all of them.

The artificial sphincter was the same as that implanted in patients with FI [15–19]. The surgical timing was different for the patients. In nine cases a perineal colostomy was performed at the same time as the APR, and a sizer was placed around the colostomy (synchronous reconstruction). Three patients had the anorectal reconstruction, with the perineal colostomy and the sizer placement (delayed reconstruction)

Table 1. Patients and methods

Pts	Sex	Indications	Tumour stage	TIMING
1	M	Rectal agenesia		Synchronous
2	F	Pelvic tumour		Delayed
3	F	Rectal cancer	T1N0M0	Synchronous
4	F	Rectal cancer	T2N0M0	Synchronous
5	F	Rectal cancer	T1N0M0	Synchronous
6	F	Rectal cancer	T1N0M0	Synchronous
7	F	Rectal cancer	T2N0M0	Delayed
8	F	Rectal cancer	T2N0M0	Delayed
9	F	Rectal cancer	T2N0M0	Synchronous
10	F	Rectal cancer	T2N0M0	Synchronous
11	F	Rectal cancer	T1N0M0	Synchronous
12	F	Rectal cancer	T3N2M0	Synchronous

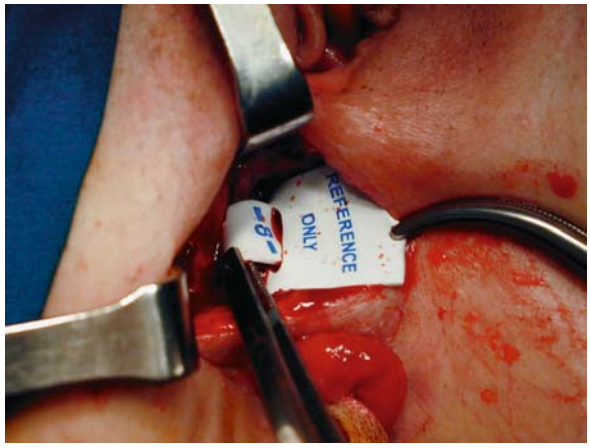

Fig. 1. Cuff of ABS implantation

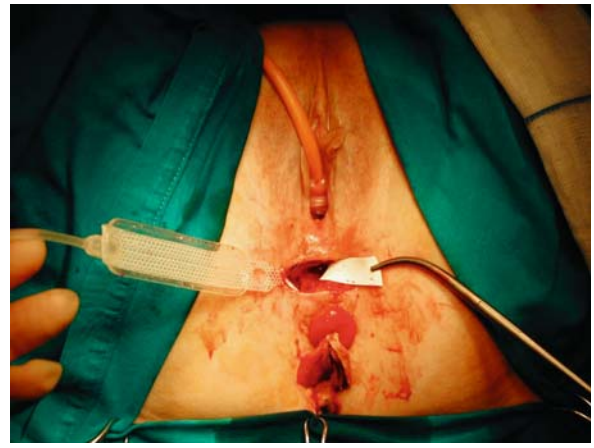

Fig. 2. Cuff of ABS implantation

some years later. A wide mobilisation of the splenic flexure was necessary to easily transpose the colon stump to the perineal plane; this part of the operation obviously being much more difficult in the delayed procedure. In the stoma patient group a pre-operative RX enema was performed to evaluate the colon length. In all patients, after two or three months the sizer placed around the perineal colostomy was removed and easily replaced with the cuff of ABS. Then the other components of ABS were implanted (Figs. 1, 2). A protective loop ileostomy was performed in all the patients to deactivate the device until the complete healing of the surgical wounds. The patients were evaluated with manometry and defecography to assess the effectiveness of the device. Manometry was performed to measure the basal pressure both with the cuff deflated and with the cuff inflated. The grade of continence was measured according to the Wexner score system [22] (Wexner score ranges from 0 in case of normal continence to 20 for total FI). A certain degree of constipation occurred in two patients and was evaluated according to the Cleveland Clinic score [23] (it ranges from 0 in case of normal evacuation to 30 as maximum grade of constipation). The patients were treated with enemas and suppositories and trained to evacuate at regular times. The time required for the cuff to inflate again after evacuation was also measured. The improvement of QoL achieved was evaluated with a faecal incontinence QoL scale (FIQoL). A QLQ-C30 questionnaire was administered pre- and post-operatively to the stoma patients and only post-operatively in all other cases [24, 25].

The follow-up length was between 40 days and 62 months. None of the patients operated on for rectal cancer developed local or distant recurrences. Three patients had the cuff explanted for skin erosion and in one patient the device was totally removed as a consequence of the radiotherapy (Table 2, Figs. 3, 4). The patient with TAR for rectal agenesia developed diarrhoea that influenced the continence score but it was successfully controlled with drugs and dietary measures. All the other patients achieved an objective good grade of continence.

The pressure with the cuff deflated ranged between 29.5 and 38 mmHg, and with the cuff inflated was between 58 and 70.3 mmHg (Table 3). The time required to reinflate the cuff ranged from 5 to 9 min. It must be considered that with TAR no comparison is possible between pre- and post-operative scores so that the use of this parameter does not provide the same objective assessment of continence reported in patients treated for FI.

All patients were trained to evacuate the neorectum at definite time intervals with the help of enemas

Table 2. Results

Pts	Complications	Continence score
1	Diarrhoea	9
2	Impaired evacuation	4
3	Impaired evacuation	4
4	Wound infection	6
5	None	3
6	Erosion → cuff explantation	
7	None	5
8	None	3
9	Erosion → cuff explantation	
10	Impaired evacuation	3
11	Erosion → cuff explantation	
12	Radioth. → cuff explantation	

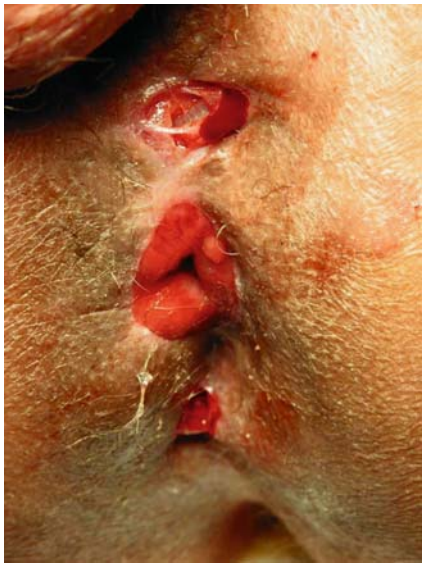

Fig. 3. Complications of cuff of ABS implantation

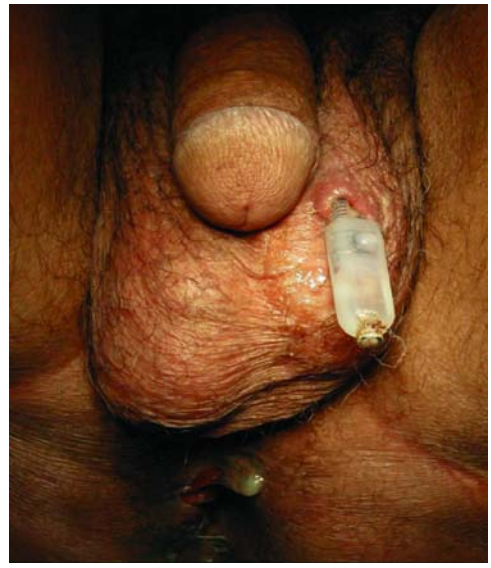

Fig. 4. Complications of cuff of ABS implantation

Table 3. Manometric results (time to reinflate the cuff**)

Pts	Basal pressure*, cuff deflated	Basal pressure, cuff inflated	Continence score
1	29.5	58	9
2	31.4	59.3	8
3	38	60	7
4	30.7	70.3	5
5	32.3	62.2	7
6	Explanted	Explanted	Explanted
7	32.6	59.8	7
8	31.2	56	8
9	Explanted	Explanted	Explanted
10	35.2	60.3	5
11	Explanted	Explanted	Explanted
12	Explanted	Explanted	Explanted

*n.v. 40–100 mmHg; **n.v. 5–8 min

and suppositories and, although three patients initially complained of impaired evacuation, an improvement of function was achieved (Table 4). After three months all patients were able to successfully evacuate the neorectum and experienced no particular difficulties in managing the device, that is, inflating and deflating the cuff of the artificial sphincter.

A psychological evaluation of stoma patients revealed a depressive status and their QoL was significantly improved by the ABS implant (delayed procedure). A post-operative evaluation of the QoL was also carried out in the "synchronous" group of patients and the results were similar to the stoma patients group. FIQoL scale demonstrated satisfaction in all cases (Tables 5, 6).

Table 4. Impaired evacuation

Pts	Score* before training	Score after training
1	3	2
2	21	7
3	17	5
4	11	5
5	9	2
6	Explanted	Explanted
7	8	2
8	9	2
9	Explanted	Explanted
10	17	6
11	Explanted	Explanted
12	Explanted	Explanted

*Cleveland Clinic Score System: range 0 (normal evacuation)–30 (max. constipation)

Table 5. QLQ-C30: delayed cases

Pts	Age	Sex	Pathology	Pre-op score		Post-op score	
				Q1–28	Q29/30	Q1–28	Q29/30
2	33	F	Pelvic tumour	41	5	33	12
7	61	F	Rectal cancer	48	4	39	11
8	61	F	Rectal cancer	47	4	31	12
Del. mean score			45.3	4.3	34.3	11.7	

Low first score (Q1–28) means good QoL. Second score (Q29/30) reports the patient self-evaluation (low scores mean bad QoL)

Table 6. QLQ-C30: synchronous cases

Pts	Age	Sex	Pathology	Pre-op score	
				Q1–28	Q29/30
1	38	M	Rectal agenesia	37	10
3	65	F	Rectal cancer	38	10
4	56	F	Rectal cancer	32	12
5	52	F	Rectal cancer	30	13
6	55	F	Rectal cancer	//	//
9	54	F	Rectal cancer	//	//
10	53	F	Rectal cancer	33	12
11	62	F	Rectal cancer	//	//
12	58	F	Rectal cancer	//	//
Syn. mean score		34.4	11.4		

Low first score (Q1–28) means good QoL. Second score (Q29/30) reports about the patient self-evaluation (low scores mean bad QoL)

Discussion

The possibility of partially restoring anatomy should lead to a more physiologic evacuation in these patients [26, 27]. Although ABS is actually more expensive than graciloplasty, it is easier to implant and more easily accepted by patients because of less difficult training. The ABS does not need the substitution of a pacemaker battery. Moreover, the results of the TAR with graciloplasty both in terms of complications and faecal continence are quite controversial. Both early and late complications have been reported. Among these, graciloplasty stenosis, fibrosis and necrosis of the muscle, perineal ptosis and perineal infection have been frequently described [28–32].

Patient selection for ABS implantation is mandatory. We believe the following conditions should be considered as exclusion criteria:

- severe cardiovascular and respiratory diseases;
- age <16 years and >75 years;
- infections;
- perineal Crohn's disease;
- advanced neoplastic disease (T3–T4, involvement of perirectal fatty tissue or perirectal lymph nodes);
- poorly differentiated tumours and anaplastic forms (because of high risk of local or systemic recurrences);
- patients requiring post-operative radiation therapy.

As for rectal cancer, patients with tumour staging T1–2N0 and early involvement of the sphincter can represent a good indication for this technique. Moreover, patients must be well motivated and both physically and psychologically skilled to manage the device.

This procedure can be performed as a synchronous or delayed reconstruction. In the first case the perineal colostomy is performed at the same time as the Miles operation and a sizer is placed around the colostomy. In the delayed procedure the perineal colostomy with the placement of the sizer is performed at least 2 years after the APR. In both the synchronous and delayed procedures, after two or three months, with a small perineal incision the sizer can be removed and easily replaced with the cuff (deferred procedure). The other components of the ABS are then implanted. The goal of this deferred procedure is both to allow a careful selection of indications on the basis of the definitive pathological report (advanced stages are excluded) and to prevent erosion of the colon with subsequent infection. In fact, the sizer previously placed around the perineal colostomy will

elicit fibrosis and a barrier between the implant and the colon wall will result. An additional advantage is economically related, as an ABS is not wasted should any infection occur in the interval between the placement of the sizer and the definitive implant.

All the patients must be followed up by manometric and radiological evaluations. Manometry is the most reliable method to achieve an objective evaluation of ABS effectiveness. Three manometric parameters must be evaluated:

- basal pressure with the cuff inflated, a post-operative significant increase of this value contributes to faecal continence;
- basal pressure with the cuff deflated, a low value of this parameter implies a wide neo-anal opening and easy defecation, whereas high pressure lead to develop symptoms of obstructed defecation;
- the time required to inflate the cuff again after the opening of the artificial sphincter to evacuate. Sufficient time is necessary to completely empty the rectum as some patients complained of impaired defecation because of a closure of the cuff quicker than the seven minutes normally required.

As for defecography, a series of X-rays allows the filling and the emptying of the cuff to be checked, as well as the correct sphincter function.

Recently, an Italian multicentre study reported disappointing long-term results after ABS implant for faecal incontinence [33]. The same complications may occur in patients who undergo TAR, that is:

- infections
- cuff deplacement
- skin erosion
- mechanical impairment of device
- obstructed defecation
- anal pain.

Constipation occurred in three cases of our series. The loss of sensitive receptors in the levator and sphincter muscles surgically ablated inevitably impairs the ability to be aware of the presence of faecal contents in the neorectum and thus activate evacuation. Clinical experience with TAR and electrostimulated graciloplasty has provided clear evidence of the constant occurrence of this complication, so that ingenious surgical solutions have been proposed to overcome the problem [34]. After any type of TAR patients must be trained to evacuate the neorectum at definite intervals of time with the help of enemas and suppositories.

Most Authors reported a high rate of infections, cuff erosions and reoperations for ABS previously implanted for faecal incontinence [33, 35]. Although in our series we reported three cuff explantations for skin erosion respectively 7, 10 and 21 months after the operation, the rate of infections was significantly lower. Attention to some technical details at operation such as location of the device far from the skin and loose around the bowel, absolute sterility and suture of a finger glove to the neo-anus that allows a finger to be inserted in the bowel without an accidental passage of faeces [19] were of the utmost importance. A further improvement in the complication rate might be explained by the presence of an ileostomy and the use of the sizer.

As far as radiotherapy is concerned, only one patient in our series received radiotherapy because of the more advanced pathological stage; this patient had the complete removal of the device 40 days after the operation. Pre-operative radiotherapy has been recently reported to significantly reduce the local recurrence rate of rectal cancer although a survival benefit remains to be proven [36, 37] and its use for early stages is also questioned. The complication rate seems to be higher when compared with surgery alone with particular reference to leakage rate and sphincter function. Miles reconstruction with the use of a sphincteral substitute is reserved for T1–2 cancer with sphincter involvement and does not require a standard anastomosis, so that neoadjuvant treatment should not be considered an absolute contraindication.

As compared with the pre-operative condition, QoL was significantly improved in patients treated with the delayed procedure. Similar good scores were also reported after the ABS implant in patients operated on with the synchronous procedure (Tables 5, 6). A careful evaluation of patients' psychological habitus is important to achieve good results.

The ABS is a valid option for reconstruction of selected patients previously treated with an APR. Nevertheless, a long-term follow-up shows that the results of the TAR performed using an ABS may deteriorate with time and may be worse than patient expectations, so that the patient should always be correctly informed and aware of the possibility of failure.

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Total Anorectal Reconstruction with Dynamic Graciloplasty

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Background

In the last few decades, improvements in surgical technique, pre-operative radiotherapy and oncological knowledge have dramatically reduced the incidence of abdominoperineal resection with permanent end colostomy (Miles' operation [1]) for low rectal cancer. Nowadays less than 5% of patients suffering from rectal cancer will undergo that operation [2], but even for these unfortunate patients the handicap of a permanent abdominal colostomy could be overcome. The *restitutio ad integrum* of the anorectal function has been a major challenge for colorectal surgeons since the first attempts by Chittenden in 1930 [3].

However, after some pioneering studies by Margottini [4] (direct perineal colostomy without continence mechanisms) and Beché [5] (direct perineal colostomy with a retrocolic sling using the anterior levator fascia), the first comprehensive report of total anorectal reconstruction following Miles' operation was published in 1976 by Simonsen et al. [6] who reported a series of 24 cancer patients with perineal colostomy and a neo-anal sphincter with an unstimulated graciloplasty according to the technique described by Pickrell et al. [7] for faecal incontinence.

This study did not, however, stimulate further attempts and in the next ten years only one paper [8] on this topic appeared in the medical literature (published in Chinese), reporting a similar rate of success (73%).

The greatest experience in the field was gained by Cavina et al. [9] who, in the mid-1980s, reawakened surgeons' interest in this operation and markedly modified the surgical technique. He first introduced the concept of temporary external muscle electrostimulation with the aim of preventing muscle atrophy and used both gracilis muscles, the first as a puborectalis sling, the other as a neo-anal sphincter. But the excellent results reported by Cavina did not overcome the scepticism of general surgeons about this operation and no other surgeons outside Italy repeated Cavina's experience for many years. The gracilis muscle is, in fact, unable to function as an anal sphincter because it cannot sustain prolonged contraction without developing fatigue and, if not stimulated for a long time, it becomes atrophic.

A strong push towards wider and more reliable application of a dynamic neo-anal sphincter using the gracilis muscle in total anorectal reconstruction came from the outstanding works by Williams et al. [10] and Baeten et al. [11] who, in the early 1990s, applied chronic low-frequency electrostimulation by an implantable pulse generator (IPG), to convert an easily fatigable muscle (like the gracilis muscle) into a fatigue-resistant one, inducing a structural and metabolic transformation of its type II muscle fibres into type I. After their initial enthusiastic reports, several colorectal surgeons around the world started to convert end abdominal colostomies to total anorectal reconstruction after Miles using the electrostimulated gracilis as a neo-sphincter, albeit with variable success [12–18].

Patient Selection and Information

Patients eligible for this operation (not of advanced age, psychologically stable and without metastatic disease) should be strongly motivated to avoid the abdominal colostomy and should be correctly and fully informed about the expected results. They should be aware that there is a significant risk of infections and that functional results are not always good, a reasonably good outcome being expected only in about 50% of cases in the long term [19], although the success rate may depend on the surgeon's experience and the number of patients operated on in each centre. But, most importantly, they should understand that a perineal colostomy is just a colostomy and that they will never experience normal defecation in the same way as they did before surgery. Another major point for correct information is that a relevant proportion of these patients have defecatory difficulty, often requiring enemas and prolonged time on the toilet to empty the neorectum.

Finally, it is ethically correct to propose this surgical option not before the cancer operation, but only after an adequate follow-up period, when the risk of cancer recurrence is lower and if the patient's motivation to dispense with an abdominal colostomy is still strong. Patients with advanced rectal cancer or non-curative resection should not therefore be offered this procedure.

Technical Notes

There are several ways to complete the operation after abdomino-perineal resection of the rectum:

1. synchronous perineal colostomy and electrostimulated graciloplasty with or without a protective ileostomy;
2. synchronous perineal colostomy and deferred electrostimulated graciloplasty with or without a protective ileostomy;
3. deferred perineal colostomy and electrostimulated graciloplasty with or without a protective ileostomy;
4. deferred perineal colostomy and subsequent electrostimulated graciloplasty with or without a protective ileostomy.

Timing of the Perineal Colostomy and Electrostimulated Graciloplasty

The perineal colostomy could be performed at the time of the Miles' operation but this is not recommended because of the risk of local recurrence. A minimum period of 2 years of oncological follow-up should be long enough to exclude patients at risk for local recurrences and to overcome the effects of adjuvant chemotherapy. Failure to follow this obvious rule can lead to a high failure rate, as recently reported by Ho and Seow-Choen [17].

The fashioning of a perineal colostomy a few years after the Miles' operation has other advantages because the abdominal colostomy can be mobilised, leaving a ring of skin around the stoma reversed to the perineum so that a skin-to-skin suture can be performed. Furthermore the exact perineal site for the neo-anus could be indicated by the patient himself during a pre-operative visit. Finally this choice will select only those patients strongly motivated to dispense with abdominal colostomy.

Even the graciloplasty can be performed simultaneously with the perineal colostomy or after healing of the suture. The need to reduce the number of operations for this procedure must be balanced against the increased risk of very fearsome infective complications. Even a simple infection at the site of the electrostimulator or electrode implant is difficult to manage and often requires removal of the expensive device. For this reason some Authors implant the electrodes and pulse generator only after the graciloplasty has healed [20].

Surgical Technique

Perineal Colostomy

After total mesorectal excision and mesentery artery ligation the rectum is removed, including the anus and levator muscles. The pudendal branches to the bladder and prostate or uterus must be spared accurately in oncologically feasible cases. The right and left colonic flexures and the descending colon must be fully mobilised in order to allow the remaining colonic stump to be lowered to the perineum through the pelvic cavity without traction. An interrupted muco-cutaneous absorbable suture is then performed to create the perineal colostomy. In cases of deferred perineal colostomy, the left abdominal colostomy must be mobilised, leaving a ring of skin and subcutaneous fat of at least 1 cm around the stoma in order to allow a skin-to-skin suture at the perineum.

This operation could be performed laparoscopically to reduce patient discomfort and for cosmetic reasons.

The fashioning of a protective ileostomy could be useful to prevent the high risk of perineal wound infection, particularly when the electrode implantation is performed at the same time of perineal colostomy [21].

Transposition of the Gracilis Muscle

On the basis of anatomical and clinical studies on the vascular supply to the gracilis muscle, Williams advocated interruption of distal small arteries to the gracilis muscle 4 weeks before the muscle transposition to enhance the intramuscular anastomosis and prevent necrosis [22], but this is not considered mandatory by other Authors (like Baeten and Cavina) based on their large clinical experience.

The patient is placed in a modified Lloyd–Davis position with the dominant leg abducted and extended. The position of the thigh will be changed (adducted) during the muscle wrapping around the anus to favour this manoeuvre. Under systemic antibiotic prophylaxis, after positioning the urinary catheter, the gracilis muscle is isolated by means of 2 or 3 longitudinal incisions on the medial surface of the thigh and the tendon is cut as distally as possible, at the

medial shaft of the tibia. Attention should be paid to prevent damage of the main *saphenous* vein. The main vascular and nerve pedicle is carefully checked under the *abductor longus* muscle with the help of a disposable nerve stimulator. This procedure enables full mobilisation of the muscle which is then passed through a previously prepared subcutaneous tunnel between the perineum and the incision on the thigh (passing Scarpa's fascia) and around the anus through another tunnel created anteriorly and posteriorly with two lateral peri-anal incisions. Care should be taken at this stage to prevent any twisting of the muscle. The shape of the gracilis loop around the anus varies from an alpha to a gamma or epsilon configuration, depending on the length of the muscle and the surgeon's preference.

A "split sling technique" version of the electrostimulated gracilis was proposed by Rosen et al. [16] to obtain an optimal muscle wrap around the anus. In this technique, the tendon of the gracilis is passed through the distal part of the muscle before its insertion into the ischial tuberosity.

The distal tendon is fixed to the medial side of the homolateral or controlateral ischiatic spine with 2–3 non-absorbable stitches using a J needle. Direct fixation to the skin is preferred by Cavina et al. [9]. The thighs are kept adducted for at least 3 days after the procedure and antibiotic prophylaxis (metronidazole+cephalosporin) can be continued for 3–5 days post-operatively.

Electrode Implantation

The electrodes should be implanted at the time of muscle mobilisation. Deferred electrode implantation after graciloplasty is quite difficult to perform although possible.

Different types of electrodes have been used for stimulating the muscle:

A four-plate electrode (Resumè quod, mod. 3587A Medtronic Inc., Minneapolis, MN, USA) or a two-plate electrode (Nice Implant®, Ft Lauderdale, FL, USA) were originally used by Williams et al. [23]. This lead is fixed with non-absorbable sutures directly on the main trunk of the gracilis nerve, where it lies on the *abductor magnus* muscle far from the gracilis; the rationale for this solution is to achieve simultaneous activation of the motor units with the minimum impulse voltage, thus lengthening the life of the battery.

Baeten et al.'s [11] and Cavina et al.'s [12] prefer the use of a couple of intramuscular flexible coil platinum iridium electrode wires (model 4300 Medtronic Inc., Minneapolis) (cathode) passed perpendicularly through the muscle very close to the entry of the main branch of the nerve and another electrode (anode) positioned similarly about 4 cm distally and sutured to the epimysium. This is the technique now generally preferred because it is easier to perform and poses less risk of electrode dislocation. Furthermore the theoretical advantages of the four plates over the wire electrodes have not been demonstrated in a retrospective comparative study [24].

The plate or wire electrodes are then passed subcutaneously and connected to the IPG. The interposition of an extension set (mod 7495-51 Medtronic Inc., Minneapolis) was necessary using the four-plate lead, which was originally designed not for this purpose but for spinal stimulation.

Implantation of the Pacemaker

After connection, the IPG INTERSTIM™ (mod 3023, Medtronic Inc., Minneapolis) is placed in a subcutaneous pocket which must be easily accessible to the patient, and also as far as possible from bone protuberances (ribs and the iliac spine) or scars. The excess wire is rolled up under the IPG, which is then sutured to the fascia with absorbable sutures.

Electrostimulation Technique

Electrostimulation can be started 2–4 weeks after the operation, when the perineal wounds have healed and the gracilis tendon is firmly sealed to the ischiatic bone. The electrical parameters can be programmed by a portable tele-neuroprogrammer (N-vision MEDTRONIC) according to two different protocols [25].

a. *Continuous electrostimulation*: impulse width 210 ms, minimum voltage required for the full muscle contraction, increased frequency from 2 Hz for the first and second week, to 5 Hz for the third and fourth week, to 10 Hz for the fifth and sixth week, then 15 Hz indefinitely (24 h a day).
b. *Cyclic electrostimulation*: impulse width 210 ms, minimum voltage required for the full muscle contraction, fixed frequency of 15 Hz, ON period of 2 s and OFF period of 6 s in the first 2 weeks, ON period of 2 s and OFF period of 4 s during the third and fourth weeks, ON period of 4 s and OFF period of 4 s during the fifth and sixth weeks, ON period of 4 s and OFF period of 2 s during the seventh and eighth weeks, permanently ON (24 h a day) thereafter.

Both methods of electrostimulation have been shown to be effective in inducing a fast-to-slow muscle conversion in an experimental study on rabbits [25]. After the muscle conversion to a fatigue-resist-

Table 1. Outcome after total anorectal reconstruction with dynamic (electrostimulated) gracilis neo-sphincter

Authors	Year	Patients	Success	%	Procedure
Seccia et al. [12]	1994	9	9	100	Double gracilis
Mander et al. [13]	1996	12	8	67	Single gracilis
Geerdes et al. [14]	1997	15	8	64	Double gracilis
Altomare et al. [15]	1997	4	2	50	Single gracilis
Rosen et al. [16]	1998	18	10	56	Single gracilis
Violi et al. [18]	2004	16	12	75	Double gracilis
Ho, Seow-Choen [17]	2005	17	10	58	Single gracilis

ant muscle is completed, the patient is provided with a remote control device (portable tele-programmer mod. 3031, Medtronic Inc., Minneapolis) and instructed to switch the IPG OFF when he/she feels the stimulus to evacuate and switch it ON again at the end of defecation. The remote control device also enables the patient to increase or decrease the voltage within a programmed range.

Post-Operative Complications

Electrostimulated graciloplasty for TAR after Miles is still affected by a worrying percentage of post-operative complications which can affect the overall success rate (Table 1). The number of complications per patient after dynamic graciloplasty for faecal incontinence or total anorectal reconstruction was 2.9 (range 1–9) in Sielezneff et al.'s [26] experience and the total complications numbered 138 in 128 patients and 68 in 27 patients in Madoff et al.'s [27] and Wexner et al.'s [28] experiences, respectively.

The more sophisticated the procedure, the more likely the occurrence of complications. In this operation complications can be related to:

1. *Neo-sphincter construction*. The most frequent complication is perineal infection, which occurs in about 10–30% of cases but can usually be managed conservatively with abscess drainage and antibiotics. Other, less frequent complications include tendon detachment from the ischiatic tuberosity and tendon necrosis. In the first type re-attachment of the tendon is usually feasible, whereas in the second the transposed muscle is no longer serviceable. Perineal colostomy may also be complicated by stricture [29], often requiring further surgery.

Another possible complication can occur at the site of muscle mobilisation with seroma formation in the thigh or persistent pain.

2. *Electronic device-related complications*. The most fearful complication is infection. As with all foreign bodies implanted in the human body, the occurrence of prosthesis infection is possible, difficult to manage, and often requires complete removal of the device itself. Electrode displacement, sometimes with external expulsion, was a relatively common complication using the four-plate electrode for direct nerve stimulation [30].

Skin erosion by the pacemaker can also occur if it is implanted too superficially, or close to bone protuberances, or if the patient loses weight. Implanting the pacemaker at the level of the waistband or too close to bones can cause pain. Albeit rarely, failures of the electronic devices have been described including electrode breakdown, early battery rundown and accidental deactivation of the pacemaker.

3. *Functional complications*. The occurrence of faecal incontinence or obstructed defecation can be considered functional complications after this operation. Although some degree of both may be well tolerated by patients, excessive incontinence or constipation may severely affect their quality of life, sometimes dictating a return to an abdominal colostomy. Soiling is a common finding due to the mucosal exposure in the perineum, but true faecal incontinence may result from insufficient increase of neo-anal pressure during muscle stimulation. On the contrary, obstructed defecation may be a consequence of neo-anal stricture or rectocele, but most commonly of a combination of factors due to the anatomical and functional changes induced by the surgical procedure in the perineum, including the loss of fine proprioceptive and somatic (anal) sensitivity [31], the loss of the rectal ampulla and part of the pelvic floor muscles, and the reduced propulsion motility of the transposed colon compared to the rectum [32]. To overcome these problems, in addition to the perineal colostomy, Saunder et al.'s [33] proposed a defunctioned colonic conduit for antegrade enemas or, more recently, a Malone antegrade continent enema even without a neo-anal sphincter mechanism [34].

Evaluation of the results of electrostimulated graciloplasty for total anorectal reconstruction after Miles' operation is extremely unreliable because almost all the reports deal with small series of patients, retrospectively analysed with significant variations in the technique used (double *vs.* single gracilis, nerve *vs.* muscle stimulation, the use of dif-

ferent devices, different electrodes and protocols for muscle conversion) but, most importantly, there is no universally accepted definition of the outcome. Perfect continence and defecation are virtually impossible to achieve in these patients, so that some degree of incontinence or the need for regular use of enemas to empty the neorectum are still considered successful outcomes. Only a few recent papers have adopted scoring systems to define the severity of incontinence and no purpose-designed quality of life (QoL) index has yet been introduced. Improvement of QoL should be the real aim of this operation.

Comments

Continence is far more than a sphincter mechanism; it is a complex physiological function involving the sigmoid colon, the rectum and its compliance, as well as the anus, the sphincters and pelvic floor musculature, the integrity of the afferent and efferent nervous autonomic and somatic pathways with their connections to the central nervous system and, finally, the characteristics of the faeces. A perfectly functioning dynamic neo-anal sphincter could restore just one of these factors after irremediable damage or eradication by surgery.

The major concern for surgeons facing this problem has always been control of the passage of stools (faecal continence), without worrying about the other side of the same coin: the ability to properly expel faeces (defecation).

A perineal colostomy with a dynamic neo-anal sphincter using the gracilis muscle has been demonstrated to be a feasible option for selected groups of patients who are strongly motivated to dispense with abdominal colostomy, but these patients should be fully informed and aware that, apart from the possible complications, a perineal colostomy is not a new normal anus and total anorectal reconstruction cannot reproduce a fully normal anorectal function. Not only may continence be incomplete, but rectal sensation is usually lost and defecation may also be troublesome and require daily enemas.

With this in mind one could argue whether these patients are “continent” or “constipated”. In fact they could falsely be considered continent because they cannot defecate except by means of daily enemas rather than because they are able to prevent the passage of faeces and postpone defecation until the right time and place. However, although they are often more content than continent, patients with total anorectal reconstruction very rarely wish to return to an abdominal colostomy even if the perineal colostomy function is far from perfect.

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Salvage Surgery After Recurrence

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Introduction

Recurrence of the disease, obviously, represents the major problem in patients who undergo "curative" resection for rectal cancer, with published rate ranging from 3 to 50%. Most relapses occur within the first two years of follow-up [1–4].

Depending on the site of the recurrence, it can be local or distant. It also can be solitary or diffuse. In terms of potential surgical cure, the best results are achieved with solitary, localised metastases.

The most common sites of the solitary metastases are pelvis, liver and lung, with a fairly even distribution among these three sites [5]. Other sites of localised metastases can be peritoneum, lymph nodes, brain, bone, abdominal wall, ureter and kidney. These sites are less common, but not as amenable to resection.

The Definition of Local Recurrence

The definition of local recurrence is clinical, radiological or pathological evidence of recurrent rectal carcinoma in the soft or bony tissues of the pelvis, with the exception of the ovaries [6], including patients with isolated local recurrence as well as those with local recurrence in association with distant metastatic disease [7].

Another definition of recurrence is a regrowth of the adenocarcinoma at the resection site at least three months following radical resection, either as isolated local disease or in addition to distant metastases [8].

In this chapter the focus of our interest will be recurrent disease localised inside the minor pelvis, which presents the most difficult and dangerous, most often late complication of surgery for rectal cancer.

Influential Factors in Genesis of Local Recurrence

Local recurrence has different features, depending on several factors: tumour characteristics, patient constitution, and surgeon's knowledge and ability.

Tumour characteristics, well known to affect the risk of local recurrence, are: location, size, mobility and gross appearance – these are the first and easiest to be assessed. In order to evaluate more easily the impact of fixation of the tumor for the surrounding structures, recurrent tumours are classified as: F0, non-fixed; F1, fixed to one side; F2, two sides; and F3, three or more sides [9]. Afterwards, the pathohistological report gives us more data: grade, stage and the potential presence of lymphatic, venous or perineural invasion. In addition, aneuploid tumors and those with a mucinous component have a negative impact on survival [10].

Patient constitution has two groups of risk factors. The first group consists of those that make surgery technically more difficult – narrow "male" pelvis, obese patients; it has also been noted that irresectability is earlier suspected or diagnosed in male patients [11]. The second group contains factors with negative influence on immunological status of the host – all types of immunodeficiency disorders (AIDS for example), some other systemic disorders, elderly patients and other non-related serious conditions.

The surgeon also plays an important role in genesis of local recurrence. Surgery for rectal cancer is difficult, and the surgeon and entire team of the institution where the patient is treated influence its results [12]. The results of the Stockholm trial and similar studies showed that high-volume surgeons in high-volume hospitals had significantly lower percentages of local recurrence (in the Stockholm trial, the local recurrence rate was 4% *vs*. 10% when comparing high- and low-volume surgeons, respectively [6]). Also, surgeons who underwent certain basic training more frequently performed TME, sphincter-saving operations and pre-operative radiotherapy (PRT) [6].

Initial Treatment of Rectal Cancer

Local recurrence has different characteristics depending on the original type of "curative" surgery. Furthermore, the surgical technique directly influences the local recurrence rate in patients with potentially curable disease. The main surgical modalities in the treatment of rectal cancer depending on the number of various factors are: anterior resection (AR), abdominoperineal resection (APR), local excision and, sometimes, Hartmann's procedure.

Regardless of the type of "radical" procedure, some basic, well established, rules of rectal cancer surgery are to be followed: total mesorectal excision (TME), distal clearance, high ligation of IMA, excision of the lymphovascular "baring" segment, preservation of the vegetative pelvic nerves. Together with these rules we will address another important factor for predicting local recurrence – circumferential margin of resection (CRM).

TME is the well established "gold standard" of rectal cancer surgery, and it includes a meticulous sharp dissection of the avascular "holy" plane between visceral mesorectal fascia and endopelvic fascia under direct vision [13, 14].

Distal clearance has been the subject of different discussions and speculations over the last few decades, concerning the radicality of the procedure. There is no question that the "5 cm rule" is, only a historical fact now. The works of Madsen and Williams [15,16] showed that, distally, tumour rarely spreads. Thanks to that, sphincter-saving procedures became possible, provided there were no technical limitations. Even low intersphincteric resections showed no increase in local recurrence when compared to APR [17].

CRM is the most important predictive factor in genesis of local recurrence. Involvement of CRM by tumour in rectal cancer is the only pathologic variable that independently influences both survival and local recurrence. A tumour that has a lateral clearance less than 1 mm has a much greater probability of recurrence (3.5 times greater risk). It also doubles the risk of death. The accuracy of CRM status in predicting the likelihood of local recurrence is 75%. The percentage of local recurrence was 38.2 *vs*. 10% when comparing involved and uninvolved CRM margins, respectively. Five-year survival was also influenced by CRM margin (72 *vs*. 29% when comparing uninvolved and involved CRM margins) [18–21].

Local recurrence in patients who underwent AR can be anastomotic or localised elsewhere in the pelvis. Anastomotic recurrence rarely originates from the mucosal suture line, as may seem logical, but it originates from the wall of the bowel and is often peri-

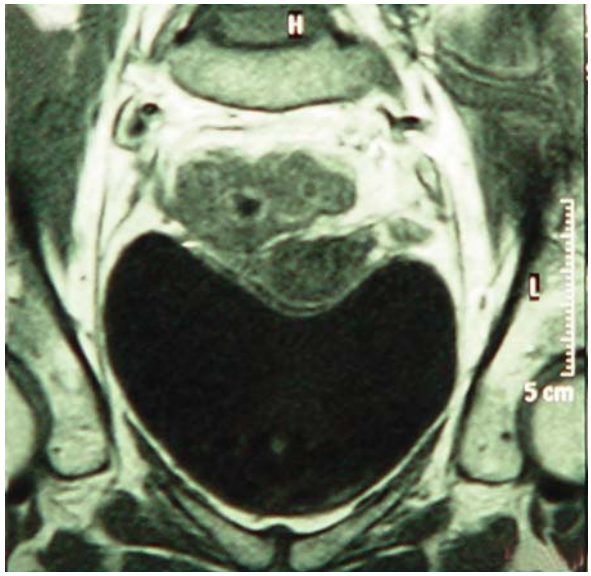

Fig. 1. NMR scan of an anastomotic recurrence after incomplete TME

anastomotic [22]. A "good" aspect of this type of recurrence is that, in contrast to APR, it provides more options for follow-up (digital, endoscopical examination, biopsy if necessary and it can become symptomatic earlier). The reasons for local recurrence in this type of operation can be found in the biology of the tumour, the stage of the disease and in technical aspects of the surgical procedure. The stage of the disease is, perhaps, the most illustrative: stage I of the disease, according to TNM classification has 5-year recurrence rate of around 10%; stage II, approximately 24%; and stage III about 41% [23].

Some Authors [5, 24] report much better results of salvage surgery in the group of patients treated in other institutions, where well known oncological principles (TME) of the surgery of the rectum were not completely conducted. This was explained with the longer period of time needed for tumour to infiltrate the surrounding structures, in the case of incomplete mesorectal excision (Fig. 1). The infiltration of these structures makes any attempt at salvage surgery much more difficult, and sometimes impossible. Nevertheless, symptoms of the recurrent tumour within the pelvis after the initial operation with incomplete TME occur much faster than in those with TME [8, 14, 25].

Salvage surgery after APR is always more difficult [13, 26], and the percentage of local recurrence is much higher [27]. Curative salvage surgery is possible in a significantly lower number of cases. There are several factors that contribute to this. Usually, patients who undergo this type of operation have

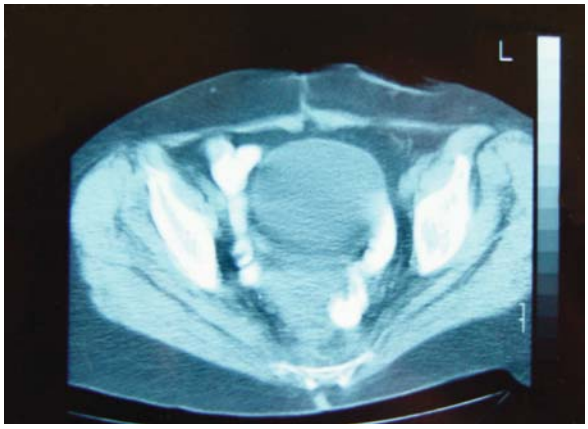

Fig. 2. CT scan of local recurrence after APR, localised in the place of previous tumor, not infiltrating the surrounding structures

larger tumours in more advanced stages. Furthermore, surgical manipulations are much more limited in attempted salvage surgery and normal anatomy is much more violated. Also, follow-up of these patients is much more difficult [13]. Physical examination is not easily feasible. In women, vaginal examination (especially endovaginal endosonography) is often very useful in detecting local recurrence; in men the only means of follow-up are radiological methods (CT, NMR, PET scan) (Fig. 2). Also, the asymptomatic period in these patients is much longer (no apparent bleeding or obstruction).

Salvage surgery after local excision is not uncommon. Different studies report a rate of salvage surgery that ranges from 22 to 100% [28–30]. For patients in stage I of the disease, local excision, in recent years, has increasingly become the therapy of choice. T1 and T2 tumours can be treated with local excision but only in certain strictly defined indications. T2 tumours have a much greater risk of local lymph node involvement, thus are much more amenable to locoregional recurrence, and are reserved for patients that are not in a condition to undergo "radical" treatment. Despite all precautions [31], estimated 5-year local recurrence rate is around 28% compared to a much lower percentage after AR in the same stage of the disease. Immediate salvage surgery is mandatory if histopathology results are unfavourable. Poor prognostic factors in pathohistology report are: tumour invasion of muscularis propria, positive margins of resection, poor differentiation or lymphovascular invasion. The results after immediate salvage surgery are much better than in surgery for already existing local recurrence [32].

If pathology results are favourable, close follow-up is mandatory (every two months for 3–4 years, occasional endorectal ultrasound (ERUS)). It should be noted, however, that results after this type of salvage surgery are less favourable than after initial "radical" surgery [33]. Though salvage surgery may appear futile, around 50% of patients with local recurrence have a solitary tumour inside the pelvis, and they are candidates for a "second look" procedure. However, the number of patients that can be resected for a cure is less than 50% (between 30 and 40%) and median survival of these patients varies from 21 to 36 months [34–36].

PRT is very important in the treatment of distant rectal cancer. After PRT, combined with TME, the local recurrence rate is significantly lower. In the Dutch trial [37], excellent results were achieved concerning local recurrence. After TME alone, 2-year local recurrence rate was 8.2%, and after TME combined with PRT, 2-year local recurrence rate was 2.4%. However, a number of studies [38] showed that survival after local recurrence in patients treated with PRT was reduced. This is explained by the fact that local recurrences after PRT may be treated less aggressively, because maximal dose radiotherapy is no longer possible as part of multimodality treatment. It is also stated that the recurrences occurring after PRT are frequently associated with distant metastases.

Follow-Up

As mentioned at the beginning of this text, close follow-up is mandatory for patients who undergo surgery with curative intent. Other very important factors that should closely be monitored during the follow-up are metachronous tumours, other malignancies and distant metastases [22]. Metachronous tumours and other premalignant lesions should be mentioned here because their early detection offers a chance of a cure.

Patients with rectal and colon cancer are also amenable to other malignancies (breast, gynaecological, lung) and investigations to discover those should be also included in the follow-up.

Once more we should highlight several factors very important for good and reliable follow-up. The most important factors that can stratify risk groups of these patients are: stage of the disease, as mentioned; invasion into adjacent structures; tumour fixation and grading; mucinous component of a tumour; and adjuvant treatment. Another factor that is very important, but difficult to ascertain, is the surgeon [39].

Close follow-up of patients should be maintained for three, not two years. In order to rationally distribute the resources, patient should be divided into three risk groups and followed accordingly [40].

Diagnosis of Local Recurrence

The early detection of local recurrence is one of the main goals of follow-up. Most relapses, when discovered, are either locally extensive or widespread disseminated, and occur, as mentioned, within a 2-year period from the initial "curative" operation. However, a small number of patients are in good general shape, with a surgically resectable recurrence, offering a chance for potentially curative resection.

Early detection of the local recurrence can be achieved by a combination of history, physical examination, CEA and Ca 19-9 measurements, endoscopy and imaging (CT, NMR, FGD-PET scan, ERUS) [41, 42]. In any clinical situation, there is frequently a single test that gives the physician the first hint of recurrent cancer.

Usual symptoms of a recurrent tumour are: pelvic pain (sometimes with radiation to lower extremities), rectal bleeding and change in bowel habits. For easier classification and assessment of treatment and prognosis, we can divide patients into groups according to symptoms as: S0, asymptomatic; S1, symptomatic, without pain; S2, symptomatic with pain [9].

It must be noted that a significant number of patients (around 50%) appear to be asymptomatic, despite evident recurrent tumour; certainly, if a patient complaints of a number of non-specific symptoms, the physician's index of suspicion should increase.

Physical examination can reveal a palpable mass within a minor pelvis. Digital examination may be very useful in detecting recurrence, which may be amenable to further surgery.

A review of symptoms and physical examination can reveal recurrence in 21% of cases [43].

Also, CEA level should be monitored regularly and its significant rise can lead to further investigations in early detection of local recurrence [22]. The sensivity of the CEA serum test ranges from 43 to 98% (the ability to predict recurrence when the serum CEA is elevated pre-operatively); the specificity of a test is higher, ranges from 70 to 90% (not able to predict the recurrence if the serum CEA is normal preoperatively. [43]. Carlsson et al. [41] reported accuracy for CEA estimation of 84% if the upper limit was set at 7.5 ng/ml. Other Authors [43] defined an abnormal CEA assay as three progressively rising CEA values over post-operative baseline with at least one value over 10 ng/ml.

Computed tomography (CT) may provide useful anatomic information when evaluating hepatic metastases, but has limited accuracy in predicting resectability for cure because of its failure to detect other small lesions in the liver, or metastases elsewhere in the body [44]. Also, the evaluation of CT scans should be taken with caution, because of a significant percentage of false-positive results in detecting recurrent disease, especially in the liver and the pelvis [43].

Magnetic resonance imaging (MRI) may be more sensitive than CT in detecting direct invasion of the sacrum in patients with pelvic tumor recurrence, but CT nor MRI are neither so successful in differentiating pelvic recurrence from post-operative fibrosis [44].

Fluorodeoxyglucose positron emission tomography (FDG-PET scan) is a relatively new, very useful procedure that exploits the increased rate of glycolysis in tumour cells (Fig. 3). It can successfully distinguish scar tissue from tumour tissue, which can prevent an unnecessary "second look" surgery [42]. Schiepers et al. [45] compared CT and FDG-PET in the evaluation of 74 patients for recurrent colorectal

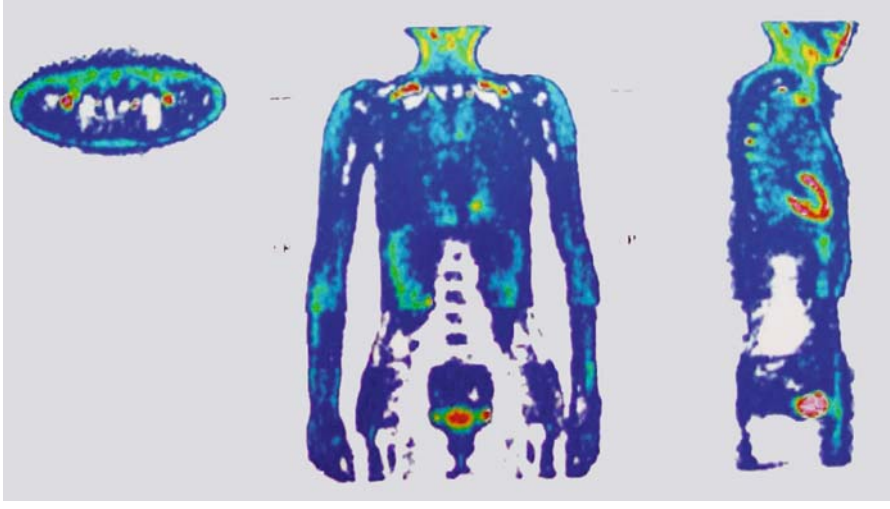

Fig. 3. PET scan showing local recurrence inside the minor pelvis

cancer and found specificity and sensitivity of FDG-PET to be much better (98% and 92%) than those of CT (60% and 72%).

A number of other diagnostic methods are available, and in some cases of crucial importance in deciding whether the patient is a candidate for curative procedure: barium enema, full lung tomography, intravenous pyelography (IVP), liver, spleen and bone scintigraphy.

Some new diagnostic tools are being evaluated, for example, carcinoembryonic antigen radioimmunodetection of colorectal cancer recurrence. This is a method compatible to CT scan and potentially can help in avoiding more invasive diagnostic methods [44]. Lechner et al. [46] report an overall accuracy of 91.6% in detecting recurrent colorectal cancer, which is superior to the results that could be obtained by the means of CT scan and/or endoscopy. Also, immunoscintigraphy detected more lesions in extrahepatic areas, compared to CT scan.

In ideal circumstances a diagnostic laparoscopy could provide highly accurate information, and help in avoiding further, more invasive surgery. However, aside from its invasive nature, sometimes it is very difficult to explore all areas of interest without excessive manipulation.

When all other, non-invasive diagnostic methods fail to confirm the existence of highly suspectable recurrent tumor, "second look" surgery is indicated.

Surgical Treatment of Recurrent Disease

Local recurrence of rectal carcinoma is a great challenge for a surgeon. Contrary to the majority of other locally recurrent tumours in the digestive system, it is possible to radically remove locally recurrent rectal cancer. Based on results from a number of different Authors [47–49], 5-year survival after re-resection is 2–13% of all patients, with locally recurrent cancer, both alone and associated with distant metastases, we can say that the goals of this kind of surgery are: palliation of symptoms, a good quality of life and, if possible, cure with low treatment-related complication rate.

The ideal goal of salvage surgery is to accomplish en bloc R0 resection, if it is technically feasible and safe. Palliation can also be a very important goal of re-resection, preferably without extensive surgical procedures, unless disabling complications of sepsis or bleeding are an issue.

The decision for salvage surgery should be made on the basis of:

- Patients general health – the patient should be fit enough for potentially extensive surgery.
- Necessary surgical expertise should also be available for these operations, which should be undertaken in specialised centres where a multidisciplinary team is available [41].

The most important thing in this matter is to decide when not to operate. The first and most obvious contraindication for surgery is "frozen pelvis", the condition where recurrent tumour involves all structures of the minor pelvis, including the pelvic walls. The next contraindication is clinical or CT evidence of invasion of the pelvic nerves, lymphatics or veins, or ureter bilaterally (as indicated by the presence of sciatic pattern of pain, unilateral swelling of the lower limb and bilateral hydronephrosis, respectively). Also, evidence of involvement of the lateral pelvic sidewalls and/or upper sacral marrow, and/or S2 is an absolute contraindication for surgery [8].

Every surgical procedure begins with an explorative laparotomy. Peritoneal seeding, unexpected liver metastases and invasion of para-aortic lymph nodes are, in general, contraindications for continuing with a procedure. It is recommended to avoid injury of critical structures before the decision on resectability is made.

Pelvic recurrences are usually amenable to resection if they are strictly anterior or posterior. Lateral sidewall involvement diminishes a chance for R0 resection, as well as involvement of two pelvic walls simultaneously (fixation degree F2). Recurrent tumour that occurs below S2 level is amenable to resection by distal sacrectomy; unfortunately, the existence of tumour in this location usually excludes R0 resection. Similarly, unilateral tumour involvement of blood vessels distal to the aorta may be resectable; bilateral affection of these structures with the recurrent tumour is a contraindication for radical resection. When prostate or base of the bladder are minimally adherent to the recurrent tumour and have good function, it is preferable to attempt combined external-beam radiotherapy (EBRT) with infusional 5-FU, followed by organ-preserving resection and intraoperative radiotherapy (IORT). The alternative to this is pelvic exenteration. In cases of more advanced disease and the existence of severe postoperative and post-irradiational adhesions, this cannot be avoided.

Another downside of surgery for recurrent rectal tumour is the problem of intestinal continuity. It is rarely possible or reasonable to create another anastomosis in the kind of surroundings that are at high risk of another relapse. In some series of patients treated for local recurrence [50], up to 93% of them ended up with permanent colostomy. Nevertheless, sometimes, in highly motivated patients with favourable local findings (mucosal anastomotic recurrence), it is possible to perform a low colo-anal anastomosis. To perform a low anterior resection

with anastomosis, in these situations moderate doses of pre-operative EBRT and chemotherapy are needed. Unfortunately, usually, a previous low AR is being converted to an APR, and previous APR to an abdominosacral resection or pelvic exenteration.

If at the end of resection it is decided that post-operative EBRT in needed, vascular clips should be placed in the area of peritumoral fibrosis or residual tumour tissue [51].

Extensive procedures employed in the treatment of local recurrence carry significant risk. Patients suffer significant blood loss, morbidity and mortality, and longer hospital stays and operative times. Post-operative complications also occur: infectious disease (sepsis, intra-abdominal abscess, enteric fistula, wound infection), urinary disease (fistulous communications with other organs, stenosis, anastomotic leak) and bowel obstruction [52]. The incidence of complications after abdominosacral resection, for example, according to some Authors, is higher than 80%. The most common are: perineal wound complication (48%) and urinary retention/incontinence, followed by peritonitis, pneumonia, pyelonephritis and different fistulous communications [53]. Mortality rates after these complicated procedures are less than 5% [8].

Non-Surgical Treatment of Local Recurrence

Although surgery plays the major role in therapy for recurrent local disease, other modalities of therapy should be considered. Maintenance of chemotherapy as a component of an aggressive treatment approach is recommended, because a local relapse is a prelude of distant metastases in about 50% of cases [54].

Radiotherapy in all of its modalities deserves an important place. Reduction of pain and bleeding was achieved in the majority of patients, whereas a response to other pelvic symptoms was not apparent. Unfortunately, the duration of effective palliation is achieved for only about one third of the remaining life span of the patient [55]. Also, complications of this mode of therapy are not to be disregarded [56].

In conclusion, EBRT and IORT, when combined only with R0 resection, improve results of therapy [56].

Prognostic Factors

It is interesting to review all factors mentioned (pre-operative, operative and post-operative) and establish their influence on post-salvage survival rates.

Patient's age, gender and the initial stage of primary tumour do not appear to change post-resection survival rates [50]. Prior APR, presentation with pain, elevated CEA levels and unresectable disease are adverse factors. Completeness of resection strongly influences survival, which is significantly shorter in R2 than in R0 and R1 cases. R0 resection, of course, correlates with the best results.

Patients with prior APR have a significantly worse prognosis than those with AR. They more frequently present with pain and elevated CEA levels. These patients also experience longer period between primary and salvage operation. This is explained with no possibility for digital examination or sigmoidoscopy. It's also impossible to observe changes in bowel habits. The reported resectability rate after APR is 60% and after AR is 86% [50]. But on the positive side, in the case of resectable disease, there is no statistically significant difference in post-salvage survival rates between APR and AR, although results after AR tend to be better [47]. As mentioned, the best results in salvage surgery are achieved after local excision when the indication for surgery is an unfavourable pathohistological report. In other cases, the most favourable outcome is achieved with patients who had recurrent disease within the bowel wall [50].

Many attempts have been made to determine the value of prognostic predictors for patients chosen for curative salvage surgery (St. Marks group, Mayo Clinic group). So far, no consensus has been reached. The only predictive factors that appear to be valuable, for now, are a tumour diameter larger than 3 cm and tumour fixation degree 2. However, it can be useful to follow the recommended tests: a CEA level of 9 ng/ml, if reached in non-smoker, laparotomy is indicated even if all other tests are negative [22].

Conclusions

Surgical treatment of locally recurrent rectal carcinoma after curative surgery is not always curative, but can provide good palliation of severe pain, bleeding, perforation, obstruction and sepsis. These procedures can be carried out with minimal mortality rates (0.8%) and can benefit from long-time survival benefits. More than 50% of patients could undergo a curative (R0) resection. This requires careful consideration of several of the most important factors: procedures must be carried out by an experienced, high-volume surgeon, with considerable expertise in this field; patients together with the type of salvage procedure must be selected carefully, considering all the factors listed above. Procedures should be carried out in high-volume hospitals.

Meticulous follow-up and early detection of recurrence are conditions for curative salvage surgery.

Advanced stages of disease may not always be a contraindication for operative treatment, providing a good surgical strategy and tactics.

A multidisciplinary approach and teamwork are ultimate conditions for success. Besides surgery, which is a dominant method of treatment, other modalities of therapy, namely hemio- and radiotherapy, should be included.

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Rectal Cancer and Inflammatory Bowel Disease

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Rectal Cancer and Ulcerative Colitis

Introduction and Epidemiology

The development of colorectal cancer (CRC) in patients with ulcerative colitis (UC) is related to the presence of pancolitis or an active disease, the duration and the severity of the disease. Historical global risk for CRC on UC is about 7.2% after 20 years of disease (Table 1) [1]. In a meta-analysis of 116 studies, Eaden showed that there was an increased risk for developing CRC in patients with UC (Table 2) [2]. Moreover, the risk of CRC is 8 times higher in patients with UC compared with people without UC and this risk is 20 times and 4 times higher in the presence of pancolitis or left-sided colitis respectively [1].

Precancerous Lesions and Conditions

Dysplasia is the precancerous lesion from which CRC develops [3]. More than 70% of patients with CRC on UC show the presence of dysplasia on colorectal mucosa [4, 5] with a transformation rate of 45% for severe dysplasia; for mild–low dysplasia there is less evidence in the literature to make a similar analysis [6, 7]. Furthermore, high grade dysplasia on rectal mucosa is a marker for the presence of CRC anywhere in the colon in 45% of the patients [8]. For these reasons, long-standing colitis with a history of 7 years or more warrants close follow-up.

Ullman et al. [8], in a review from the Mayo Clinic experience from 1990 to 1993, studied 18 patients with a mean follow-up of 32 months with a low-grade dysplasia; nine patients showed a neoplastic lesion (high-grade dysplasia or CRC) in the follow-up with a progression rate of 33% at 5 years. One patient developed a CRC 20 months after the last colonoscopy performed 74 months after the diagnosis of low-grade dysplasia. So, the Authors' conclusion was that a prophylactic colectomy should be performed for patients with long-standing colitis and dysplasia.

Moreover, about 25–68% of the patients with UC developed a CRC without any evidence of dysplasia; for these patients a different pattern of neoplastic growth should be hypothesised, with the need for new clinical and biological markers for transformation [4, 5, 9–11].

Sclerosing cholangitis (SC) is an additional and independent prognostic factor of CRC on UC. From a meta-analysis on 11 comparative studies, SC has been shown to be a significant risk factor for dysplasia or CRC in patients with UC [12].

Shetty et al. [13] compares two groups of patients, 132 with SC and 196 controls with UC without SC; CRC and dysplasia were more frequent in patients with SC (25 *vs*. 5.6%) and the tumours were localised more proximally and of a more advanced stage. Furthermore, the CRC related mortality for patients in the SC group was significantly higher (4.5 vs. 0%; $p<0.01$).

Similar results were obtained by Linberg et al. [14]: of 143 patients with UC followed for 20 years (19 SC), those with SC showed a predisposition for developing CRC and/or dysplasia with tumours located proximally ($p=0.02$).

Table 1. Risk of CRC and duration of the disease

Risk (%)	Duration of the disease (years)
0.7	10
3.4	15
7.2	20
11.6	25

Table 2. Risk of CRC and duration of the disease

Risk (%)	Duration of the disease (years)
2	10
8	20
18	30

Table 3. Stage and CRC on UC

CRC (%)	Dukes' stage
40 on UC	A–B
60 on UC	C–D
63 without UC	A–B
36 without UC	C–D

Habermann et al. [15] studied many biological risk factors; aneuploid DNA distribution patterns, laminin-5 gamma2 chain and cyclin A expression can identify a group of UC patients with an increased risk for cancer development (p=0.006, p=0.002, p=0.014 respectively).

CRC on UC is correlated to a more advanced stage compared with CRC without UC (Table 3).

Van Heerden et al. [16] showed that 5-year survival in 70 patients with diagnosis of CRC on UC was worse compared with patients operated on for prophylactic colectomy with incidentally diagnosed CRC (72 vs. 35%).

Connell et al. [5], in a study of 120 patients operated on for 157 CRC on UC (CRC located in the sigmoid or rectum in 67.5% of the patients) showed that five-year survival of 16 patients in whom cancer developed during surveillance was 87% compared with 55% of 104 patients who did not participate in surveillance (p=0.024).

An important issue in the diagnosis and treatment of patients with or at risk for CRC on UC is the management of the stenosis. Lashner et al. [17] studied 15 patients with stenosis on UC (3.2% of all UC); eleven patients showed the presence of dysplasia and two patients had a CRC at colonoscopy biopsy. Ultimately, six patients showed a carcinoma found at colonoscopy or colectomy. All cancers were at the site of a stricture. These findings indicate that a true colonic stricture in UC is frequently associated with dysplasia and cancer. For this reason a stricture should be considered a strong risk factor for cancer and, if dysplasia is discovered or if the stricture cannot be adequately biopsied, consideration should be given to total colectomy [17].

Surgical Options

Provenzale et al. [9] proposed prophylactic colectomy for patients with a long-standing colitis or at risk of developing CRC; this approach should prevent the need of emergency colectomy. In a comparative study of about 17 different strategies, including no colonoscopic surveillance, surveillance at varying intervals and prophylactic proctocolectomy with ileal pouch-anal anastomosis, Provenzale showed that for a 30-year-old patient with pancolitis for 10 years, prophylactic colectomy would increase life expectancy by 2–10 months compared with surveillance and by 1.1–1.4 years compared with no surveillance. Surveillance would improve life expectancy by 7 months to 1.2 years compared with no surveillance.

However, when proposing this approach to the patients we should consider that restorative proctocolectomy is a major surgical procedure. The global rate of success is 95% with a morbidity of 13–59% and a post-operative complication rate of 30–50% [18–24].

Obviously, in the presence of a diagnosed CRC a total colectomy is mandatory.

In patients with rectal cancer and UC the stage could determine the best surgical option (Table 4). In patients with stage 1–2, restorative proctocolectomy is the procedure of choice because the disease is not advanced. Surgical technique, however, is quite different because an extramesorectal approach must be chosen with a high ligation of mesenteric vessels instead of an intramesorectal dissection.

Moreover, if the choice for the type of rectal dissection in patients with a diagnosed rectal cancer is clear, in the case of prophylactic proctocolectomy in males younger than 50 years and with the presence of high-grade dysplasia, an extramesorectal excision should be carefully chosen.

The rate of genito-urinary dysfunction in males after anterior resection for cancer is 0–49% [25]; this is an acceptable rate in the presence of a certain cancer but for a prophylactic surgery it should be carefully evaluated. The rate of impotence after rectal excision for inflammatory bowel disease is lower than after excision for rectal cancer ranging from 0–25% [25–30]. The incidence of sexual dysfunction increases with age and when a mesorectal plane is preferred to close rectal plane of dissection [25].

Another important issue is the role of transanal mucosectomy. Mucosectomy theoretically eliminates the risk of neoplastic transformation in the remaining anal canal epithelium. O'Connell et al. [31] showed that even after endo-anal mucosectomy, residual of rectal mucosa remains in the denudated muscle cuff in up to 14% of the patients and in up to 7% of patients at anastomosis.

Tsunoda et al. [32] studied the incidence of dys-

Table 4. Cancer and surgical options

Stage	Procedure
1–2	Restorative proctocolectomy
(2)–3	Proctocolectomy+ileostomy
4	Segmental colectomy

plasia in the mucosal strippings from the anorectal stump of patients operated on with restorative proctocolectomy for UC or familial adenomatous polyposis. On 118 operative specimens (8 CRC on UC) 87.5% of patients with cancer showed dysplasia on the colonic mucosal compared with only 4.5% of those without cancer. Anal mucosa of patients with CRC showed dysplasia in 25% of the cases compared with only 0.9% of those without cancer. Moreover, colonic dysplasia was present in 26.3% of the patients with a long-standing colitis (more than 10 years from the diagnosis) compared with 2.6% of those with less than 10 years of disease; a similar trend was observed for dysplasia in the anal mucosa (7.9 *vs*. 0%).

However, since the first description of the double-stapled technique restorative proctocolectomy [33], there is still controversy over the risk of dysplasia and residual disease.

The pros for the preservation of the anal transitional zone (ATZ) are that it is technically easy and seems to improve function with a low rate of septic complication and sepsis-related pouch excision compared with the handsewn technique [34]. Reilly et al. [35], in a prospective randomised trial, showed that 64% of the handsewn group experienced occasional or frequent episodes of faecal incontinence compared with 38% of the stapled group with higher anal canal resting pressure (49.4 vs. 78.3 mmHg, $p<0.05$) and squeeze pressure (144 vs. 195 mmHg, $p<0.06$) in the stapled group. However, other randomised trials have failed to find functional differences between the two techniques [36, 37].

On the other hand, mucosectomy decreases the risk of dysplasia. At a follow-up of 10 years after restorative proctocolectomy, the incidence of dysplasia was 5% [38].

The risk of developing a CRC on ATZ is very low. In the literature there are four cases of adenocarcinoma arising along the rectal stump after double-stapled pouch in patients with UC [39, 40].

A correct approach is to routinely perform a mucosectomy, if a restorative proctocolectomy is performed in the presence of CRC or dysplasia; in all other cases a stapled restorative proctocolectomy is safe and a yearly digital examination with ATZ biopsy should be performed. If a dysplasia is found, a transanal mucosectomy with ileal pouch advancement is advocated [41, 42]. Functional results after restorative proctocolectomy for rectal cancer in UC are the same compared with that observed in patients without cancer.

Gorfine et al. [43] studied 45 patients with CRC on UC (14 rectal location) which underwent restorative proctocolectomy. Thirty-six of the 39 patients still alive (92%) had a functioning pelvic pouch.

Remzi and Preen [44] showed 26 rectal cancers in 1850 patients with UC (1.4%). These patients underwent a restorative proctocolectomy with mucosectomy and the oncological and functional results were good, with a five-year survival of 78% and a good to excellent pouch function at a follow-up ranging from 1 to 17 years.

Rectal Cancer and Crohn's Disease

The association of Crohn's disease and cancer is uncommon, with an overall prevalence of 0.45% [45]. Carcinoma in Crohn's disease is associated with strictures, extensive disease and onset of the disease before the age of 30 years. Sandmeier reported 3 patients with cancer in Crohn's disease from a database of 661 patients between 1993 and 2001; only one patient had a rectal localisation (signet ring cell variant) 4 years after a subtotal colectomy with ileosigmoid anastomosis [45].

Connell et al. [46], in a review on 2500 patients with Crohn's disease from 1940 to 1992, described 15 patients who developed a carcinoma of the lower gastrointestinal tract. Thirteen patients had a cancer in the upper third of the rectum (one), in the lower third of the rectum (seven) and in the anus (five patients). Patients with a cancer arising in the rectum had long-standing severe anorectal disease with a stricture in four, a fistula in four, a proctitis in one and an abscess in two patients.

Nikias et al. [47] reviewed the medical records of 16 patients with simultaneous diagnosis of Crohn's disease and carcinoma with eight rectal lesions of which two developed cancer in a defunctionalised rectum. Six patients had severe anorectal disease.

Instead of a low rate of incidence of rectal cancer, in young patients with long-standing, severe ano-rectal Crohn's disease, the fate of the rectum should be considered.

Rectal Stump

An important issue is the fate of the rectum after subtotal colectomy for UC or Crohn's disease. Johnson et al. [48] studied a series of 1439 patients with UC. A surgical resection was performed in 374 patients (26%); 172 patients underwent subtotal colectomy with mucous fistula. Ten patients (3.6%) developed a rectal cancer. In this study the cumulative risk of developing a rectal cancer in the rectal stump reached 17% 27 years after disease onset.

A similar study by Oakley et al. [49] on 288 patients having a subtotal colectomy for UC showed four patients (1.4%) who developed a cancer in the rectal stump.

Winther et al. [50] studied 42 patients with a closed rectal stump after surgery for UC or Crohn's disease. The median duration of the disease was 8.3 years (1.3–34 years). The Authors showed no endoscopic or histological signs of dysplasia or carcinoma and no mutation of p53 gene in any biopsy or lavage fluid. However, 78% and 43% of the patients showed moderate to severe mucosal inflammation and rectal stump involution respectively. For this reason a role of adjuvant markers to improve cancer surveillance in this subgroup of patients is advocated.

Conclusions

The risk of CRC developing in patients with UC and Crohn's disease are related to some risk factors. Careful follow-up should be reserved for patients with long-standing disease, early onset, extensive disease, primary SC, stenosis and a family history of CRC. For patients with Crohn's disease, strong attention should be given to young patients with extensive rectal disease.

A regular endoscopic surveillance is mandatory for the second decade of the disease, with an interval of 3 years and, after the fourth decade of the disease, annually. In the presence of one of the risk factors associated with dysplasia, a prophylactic colectomy should be considered. In patients with high-grade dysplasia or with a clear cancer, a total colectomy with mesorectal excision should be performed. Oncological and functional results after restorative proctocolectomy for rectal cancer in UC are similar to those without UC.

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Multimodality Therapy of Rectal Cancer

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Introduction

Rectal cancer represents a serious oncological problem because of its high frequency in Western countries (40 340 estimated new cases of rectal cancer in the USA in 2005, with estimated deaths of 56 290 people from colorectal cancer) with an increasing trend, and its high morbidity and mortality rate [1].

Surgery still has a major role in the treatment of patients affected with rectal cancer. Results of surgery are strictly correlated with the stage of the disease: depth of invasion of rectal wall and presence or absence of locoregional lymph node involvement. Survival at 5 years after curative rectal resection is 80% for patients in stage I, 50–60% for stage II and decreases to 30–40% for stage III cancer [2].

The main reason for failure after radical surgery in the group of patients with advanced rectal cancer is local recurrence that has an incidence reported in the literature ranging from 15 to 50% [3, 4].

Major sites of local failure are the presacral area, involving anastomosis (in low anterior resection), perineal skin (in abdominal perineal resection (APR)) and pelvic organs (bladder, vagina, prostate, etc). Radical resection of recurrence is possible in a limited number of cases, in which anastomosis only is involved, and APR or pelvic exenteration are technically feasible [5]. In other cases, where pelvic bones are infiltrated, use of palliative treatment is justified. These patients often suffer symptoms that are poorly responsive to medical therapy and mortality rates remain high.

During the past 20 years, several models of neoadjuvant or adjuvant treatment have been proposed for treatment of patients with rectal cancer (surgery differently combined with chemotherapy, radiotherapy (RT) or both), with the aim of improving overall and disease-free survival, and increasing the number of resections with free margins.

Staging

The ideal pre-operative assessment assigns patients with rectal cancer into three distinct groups: patients with early stage localised lesions where surgery alone would potentially be curative; patients with locally advanced cancers who are likely to benefit from pre-operative or adjuvant therapy; and those with advanced or metastatic disease where surgery might be modified or avoided. The presence of associated comorbidities will also influence the choice of treatment.

Patients with rectal cancer should undergo a clinical examination, blood sampling including CEA, endoscopic exam with biopsy specimen, endorectal ultrasound (EUS), magnetic resonance (MRI) or computed tomography (CT) and chest X-ray.

EUS allows clear visualisation of the layers of the rectal wall and thus enables the depth of invasion to be accurately measured. Its accuracy varies from 82 to 93% in terms of T factor in the literature. Assessment of lymph node status is less reliable, with an accuracy of 65–81% (EUS staging is defined yTN).

Inflammatory changes from previous biopsies or irradiation may reduce the diagnostic accuracy of this method whereas a stenotic lesion may limit access of the probe [6–8].

RMI or CT scans of the abdomen and pelvis are recommended as they provide additional information about the extent of the disease such as the presence of distal metastatic disease or pelvic organ infiltration.

MRI with endorectal coil exhibits similar accuracy to EUS and is superior to conventional CT in pre-operative assessment of depth of invasion of rectal cancer (accuracy 81 *vs*. 65%) and adjacent organ invasion. Furthermore, MR enables more accurate identification of nodal involvement than other imaging modalities [9–12].

Unfortunately, MRI loses these advantages in restaging irradiated tumours (accuracy 52% for T factor and 68% for N factor), with poor agreement with pathological stage of T and N factor while MR

Table 1. AJCC staging of rectal cancer [16]

Stage	T	N*	M
Stage 0	*In situ*	0	0
Stage I	1–2	0	0
Stage II A	3	0	0
Stage II B	4	0	0
Stage III A	1–2	1	0
Stage III B	3–4	1	0
Stage III C	Any T	2	0
Stage IV	Any T	Any N	1

*A tumour nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion

keeps reliable prediction of clear circumferential resection margins. It is probable that most of the inaccuracy in both T and N stages is caused by overstaging. Thickening of the rectal wall after radiation by marked fibrosis, peritumoral infiltration of inflammatory cells and vascular proliferation cannot be completely differentiated from viable residual tumour by this technique [13, 14].

During the past few years, FDG-PET has been studied in the assessment of chemoradiation response of locally advanced rectal cancer, showing good results with a negative predictive value of 100% *vs.* MRI or CT and high efficacy in detection of metastatic disease [15].

We should not forget that if removal of the rectum is contemplated, early consultation with an enterostomal therapist should be recommended for preoperative marking of the site and for pre-operative assessment of the patient (Table 1).

Surgery

The surgeon should remove the primary tumour with adequate margins: R0 are complete tumour resections with all margins negative; R1 are incomplete tumour resections with microscopic involvement of a margin; and R2 incomplete tumour resections with gross residual tumour.

Patients affected by rectal cancer are submitted to one of the following surgical procedures: transanal procedures in early rectal cancer; low anterior resection or colo-anal anastomosis; and APR in both cases, using the total mesorectal excision technique. Sacrifice of anal sphincter and a permanent stoma may adversely affect the quality of life of some patients but an inappropriate sphincter-sparing procedure may result in excessive stool frequency and faecal incontinence.

The total mesorectal technique consists of sharp dissection of the predominantly avascular plane between the parietal and visceral pelvic fascia. Anteriorly, the specimen contains the intact Denonvilliers's fascia and the peritoneal reflection. Autonomic nerve preservation requires identification and sparing of the pre-aortic superior hypogastric plexus as well as the bilateral hypogastric nerves to form the inferior hypogastric plexus anterolaterally on both sides [17].

Dutch surgeons showed that standardised application of this technique permits reduction of the incidence of local recurrence (local recurrence 8.2%) omitting adjuvant therapy [18].

The total mesorectal excision technique permits correct valuation of lymph node status and radial margin. A positive radial margin is a negative prognostic indicator with sensitivity, specificity and positive predictive values of 92, 95 and 85% respectively [19].

Locally advanced cancer should be removed by en bloc resection including any adherent tissues, as it is not possible to differentiate macroscopically between adherence of malignant invasion or inflammatory reaction. En bloc resection with clear margins of adjacent organs locally infiltrated by cancer can achieve similar rates of survival as patients with tumour T3 [20, 21].

Adjuvant Radiochemotherapy

The efficacy of post-operative radiation and 5-fluorouracil (5-FU)-based chemotherapy for stage II and III rectal cancer was established by a series of prospective, randomised clinical trials (GITSG, NCCTG, NSABP) (Table 2) [22–25]. These studies demonstrated an increase in both disease-free interval and overall survival when radiation therapy is combined with chemotherapy following surgical resection. Following the publication of these trials, the National Cancer Institute (NCI) concluded at a Consensus Development Conference in 1990 that post-operative combined modality treatment is recommended for patients with stage II and III rectal carcinoma [26].

Subsequent studies have attempted to increase the survival benefit by improving radiation sensitisation, and by identifying the optimal chemotherapeutic agents and delivery systems. The chemotherapy associated with the first successful combined modality

Table 2. Surgery vs. RCT

Trial		Local failure	5-year survival
GITSG 1986 [22]			
Surgery alone		24	44
Surgery+CRT	40 Gy/4 week+5-FU	11	59
NCCTG 1991 [23]			
Surgery+RT		25	48
Surgery+RCT	50.4 Gy/5.5 week+5-FU/semustine	14	57
Tveit et al. [24]			
Surgery alone		30	50
Surgery+RCT	46 Gy/4 week+bolus 5-FU	12	64
NSABP 2000 [25]			
Surgery+CT		13	65
Surgery+RCT	50.4 Gy/5.5 week + 5-FU/folinic acid	8	66

treatments was 5-FU and semustine. The latter is not commercially available and previous studies have linked this drug to increased risks of renal toxic effects and leukaemia [27].

In 1994, O'Connell published the results of a trial showing a 10% improved overall survival with the use of a continuous infusion of 5-FU (225 mg\m^2\day) throughout the course of radiation therapy when compared with bolus 5-FU (3×500 mg\m^2 injections in the first and fifth weeks of radiation) [28]. Authors show no survival or local control benefit with the addition of leucovorin, levamisole or both, to 5-FU administered post-operatively for stage II and III rectal cancers at a median follow-up of 7 years [29].

New effective drugs including capecitabine, raltitrexed, irinotecan and oxaliplatin have been recently investigated in combination with radiation therapy. In addition, novel targeted biological agents including epidermal growth factor receptor inhibitors and vascular endothelial growth factor inhibitors have been shown to enhance the antitumour effect of both radiation and chemotherapy and are currently being explored in initial clinical trials [30].

Side Effects of Adjuvant Therapy

The reported mortality rate in trials of adjuvant chemoradiotherapy ranged from 0.3 to 4% [23, 28]. Deaths were due principally to sepsis (40%), intestinal obstruction or perforation (50%) and peritonitis. Completion rate of treatment preview ranged from 65 to 92%.

Major acute gastrointestinal toxicity included severe diarrhoea (7–35%), nausea and vomiting, and stomatitis. Haematological side effects such as leucopenia and thrombocytopenia occurred in 5–33% of patients [23, 27]. Long-term radiation effects include radiation enteritis, small bowel obstruction (SBO) and radiation stricture [27, 29]. The high incidence of SBO after post-operative RT may be secondary to post-operative adhesions and the prolapse of small bowel loops into the irradiated pelvis and can require surgery. The incidence of SBO increases by 30–40% when the radiation fields extend higher into the abdomen. The extent of this problem seems to be related to the volume of the irradiated small bowel [31].

Patients receiving post-operative chemoradiation have more bowel movements per day, clustering of bowel movements and nocturnal bowel actions. More of these patients wear a pad and are unable to defer defecation for more than 15 minutes. They also have a higher incidence of faecal incontinence, greater use of anti-diarrhoeal drugs, more perineal skin irritation and more difficulty in differentiating stool from gas.

Improved radiation planning and techniques can be used to minimise treatment-related complications. These techniques include the use of multiple pelvic fields, prone positioning, customised bowel immobilisation moulds (belly boards), bladder distension, visualisation of the small bowel through oral contrast and the incorporation of three-dimensional or comparative treatment planning [32, 33].

At present, the adjuvant approach seems more suitable for patients affected with proximal rectal cancer, where a less accurate pre-operative staging is feasible.

Pre-Operative Radiochemotherapy

Although combined adjuvant chemoradiotherapy was standard in the USA, European centres studied the feasibility of pre-operative radiation therapy.

The principles of the neoadjuvant scheme are: higher efficacy of radiation and chemotherapy agents

in well vascularised and oxygenated tissue; lower radiation fields; and excision of irradiated large bowel and less small bowel irradiation (easily dislocated), which may reduce late complications such as SBO. Pre-operative irradiation may also cause less acute toxicity and more patients will receive full-dose radiation therapy.

The consequent volume size reduction of the tumour could lead to a lower risk of dissemination of neoplastic cells during surgical handling of the rectum, a high number of sphincter-saving procedures and a higher rate of resectable rectal cancer with free margins.

A major concern for pre-operative radiation therapy is that patients with early stage tumours or disseminated disease will often receive unnecessary treatment, necessitating improved imaging techniques that allow more accurate patient selection. Moreover, neoadjuvant treatment usually postpones definitive surgery considerably and may also be associated with increased post-operative morbidity.

RT can be administered in conventional fractionation in long course, or in short course. The conventional fractioning uses multiple fields (usually 2–4) on a tumour volume correctly conformed. Doses of 1.8–2.0 Gy/day, 5 days/week, for 5 weeks are administered, reaching a total dose of 45–50.4 Gy. During the last week of therapy an additional boost on residual tumour volume can be administered. Several trials on radiosensitive neoplasms have shown that a dose of 50 Gy is the minimal dose to eradicate micrometastasis. In the short course, doses are higher per single fraction: 5 Gy×5 days (total dose of 25) followed by surgery a week later. The supposed advantage of the short course is that reducing treatment time should prevent repopulation of tumour cells. Five doses of 5 Gy has a comparable efficacy to 45 Gy fractioned as calculated with the Cumulative Radiation Effect (CRE) formula [34]. Unsatisfying results were initially published, as pre-operative radiation therapy was used with low dose (5–25 Gy) and no benefits *vs.* surgery alone emerged [35, 36].

A randomised study of Swedish Authors [37] published in 1990 showed better results in terms of local recurrence in patients treated pre-operatively with RT *vs.* patients treated after surgery. The first group of patients were treated with short-term RT, 25.5 Gy/week, and the second group of patients underwent RT with a dose of 60 Gy post-operatively. In the first arm of the study a lower rate of local recurrence emerged *vs.* the second arm: 13% vs. 22% respectively (p=0.02). Nevertheless, the overall survival at 5 years did not reach a statistically relevant significance (42% vs. 38%, p=0.5).

The Authors noted a higher rate of acute toxicity, a higher rate of complications of perineal wound in patients treated with APR such as infection and delayed healing and a lower rate of late complications of RT such as bowel obstruction in patients treated with RT pre-operatively.

The Swedish Rectal Cancer Trial [38, 39] showed a significant increase in overall survival in patients treated pre-operatively. The study enrolled 1 168 patients; a group of patients underwent surgery alone and the other group of patients underwent short-term RT a week before surgery (25 Gy/5 days). The local recurrence rate reported in this trial was 27 *vs.* 12% respectively (p<0.001) and a better overall survival at 5 years (58 vs. 48%, p=0.004). Thus, the results of this large study once again supported the oncological paradigm that survival is improved by better local control.

A Dutch trial randomising 1 805 patients with resectable rectal cancers (stages I–IV) to a short course of radiation (500 cGy×5) followed by TME compared to TME alone demonstrated no difference in overall survival at 2 years (82% for both arms) [18]. However, local recurrence rates were significantly reduced in the RT plus TME arm (2.4%) as compared to the TME only arm (8.2%, p<0.001). Patients with stage II–III rectal cancer and patients with neoplasm localised 5–10 cm from the anal verge obtained better results from the treatment.

Because surgery is performed only one week after the completion of radiation therapy, as in Swedish trials, significant tumour shrinkage is very unlikely and one of the major goals of pre-operative treatment, the preservation of sphincter, is more likely to be achieved. Prolonging the interval between RT and surgery has been studied. The longer interval (6 weeks against 2 weeks) between radiation in long course and surgery was associated with a significantly better clinical tumour response (71 vs. 53%, p=0.007) and pathological downstaging (26 vs. 10%, p=0.005), and sphincter-preserving operations (76 vs. 68%, p=0.27) [40]. Due to the short overall treatment time, such as 25 Gy in a week, radiation therapy cannot be combined with an adequate dose of systemic chemotherapy. Thus the potential effect of radiosensitising of the chemotherapy drug to enhance local tumour response and simultaneously treat occult distant metastasis would decrease.

Several institutions have applied pre-operative radiation in conventional fractionation in the treatment of fixed T4 rectal cancer with the goal of converting them in resectable cancer. Minsky et al. [41, 42] compared pre-operative RT 50.4 Gy with or without chemotherapy with 5-FU and a high dose of folinic acid, showing that 90% of the patients with initially unresectable tumours were converted to resectable lesions compared with only 64% of those who received radiation alone. Moreover, a complete

Table 3. Pre-operative treatment and clinical response

Author	Patients	Clinical response (%)	Pathological response (%)
Chari et al. [44]	43	51	27
Habr-Gama et al. [45]	118	30.5	–
Hiotis et al. [46]	488	19	10
Crane et al. [47]	238	47	Not specified
Moutardier et al. [53]	113	–	8
Zmora et al.[49]	109	43	14

Table 4. Pre-operative treatment and results

Author	Patients	Scheme	Median follow-up	pT0 (%)	Down staging (%)	LR (%)	OS (%)
Bonnen et al. [50]	405	45 Gy+5-FU	46	–		8	81
Sauer et al. [51]	420	50.4 Gy+5-FU				6 *vs.* 13 (adjuv)	76 at 5 years
Theodoropoulos et al. [52]	88	45 Gy+5-FU/ leucovorin (LV)	33	18	41	10.2	83.9
Moutardier et al. [53]	113	45 Gy	75	8	49.5	9	79
Garcia Aguilar et al. [48]	168	45–60 Gy+5-FU	37	13	58	5	68
Nakagawa et al. [54]	52	50.4 Gy+5-FU/ folinic acid	32			17.9	60.7
Habr-Gama et al. [45]	118	50.4 Gy+LV/ bolus 5-FU	36			4.3	84.7
Chan et al. [55]	128	50 Gy+5-FU/ LV/mitomycin C	–	25	66		

pT0, pathological response; *LR*, local recurrence; *OS*, overall survival

pathological response was found in 20% of patients who received multimodal treatment. Several phase II trials of pre-operative radiochemotherapy confirmed these results such as our experience, demonstrating the feasibility of tumour shrinkage in T4 rectal cancer, allowing a higher number of curative resections [41–43] (Tables 3, 4).

Results of the CAO/ARO/AIO-94 study from the German Rectal Cancer Group have recently become available [51]. This trial started in 1995 and ended in 2002; a total of 823 patients with T3–T4 or node-positive disease were enrolled. Group A, with pre-operative radiochemotherapy, consisted in 421 patients receiving 5040 cGy in 28 fractions and 5-FU in continuous infusion and then surgery after 6 weeks; another cycle of 5-FU was given one month after surgery. In the post-operative radiochemotherapy Group B, 402 patients were recruited and experienced the same regimen post-operatively plus an additional boost of 540 cGy.

Overall five-year survival was similar in both groups (A: 76%, B: 74%), whereas local control was improved in Group A (6% of recurrence), as compared with Group B (13%). In Group A there were fewer acute 3 or 4 grade (especially diarrhoea, haematologic effects, dermatologic effects) and long-term toxic effects (strictures of the anastomoses, bladder problems, chronic diarrhoea, SBO): respectively 27% and 14%, as compared with Group B (40% and 24%). Post-operative complication rates were similar in both arms, with about 11% of anastomotic leakage of any grade in the pre-operative group as compared with 12% in the post-operative group. The rates of ileus, post-operative bleeding and delayed sacral wound healing were similar also.

The Authors concluded that pre-operative chemoradiation for advanced rectal cancer should be the preferred option because of better local control, reduced toxicity and increased rate of sphincter preservation. Based on results from phase I and II trials, the standard regimen for patients who receive combined modality therapy is continuous 5-FU infusion, and pelvic radiation. Regimens using CPT11 or oxaliplatin-based combined modality therapy plus

either continuous infusion of 5-FU or capecitabine are under active development [56].

Sphincter Preservation

After pre-operative RT, as shown, tumour is often reduced in size, is downstaged or even shrinks and sometimes also disappears and therefore may facilitate conservative surgery. Data from the literature are not conclusive with respect to how often a planned abdominoperineal resection can be converted to a sphincter-saving surgery after pre-operative radiochemotherapy. It depends also on the specialisation of the surgeon, techniques used in colo-anal anastomoses, intersphincteric resections and the length of distal margin judged as adequate (2 cm, 1 cm). There is still controversy about the place of downsizing neoadjuvant therapy and the true long-term functional outcome.

Nowadays, abdominoperineal excision seems to be performed for oncological reasons if cancer invades the anal sphincter and when R0 cannot be otherwise obtained, making sphincter-saving surgery the standard procedure for low rectal cancer [57].

Experiences of radiochemotherapy without surgery also exist in the literature, with contrasting results. Nakagawa et al. [54] did not operate on 10 patients after complete clinical response to chemoradiotherapy for middle and low rectal cancer. Eight patients presented local recurrence within 3.7 and 8.8 months, requiring salvage surgery. Two patients were disease free after 37 and 58 months. An exclusive medical non-surgical approach seemed unsafe for rectal cancer.

Other Authors [58] conclude that a complete clinical response after neoadjuvant chemotherapy is associated with an excellent outcome in terms of five-year overall and disease-free survival also without surgery (respectively 100% and 92%). Surgery may in this context only increase the morbidity and mortality rates and negatively influence quality of life with the creation of a temporary or definitive stoma.

Some Authors have performed local excision after chemoradiation with apparently good results, especially initially after patient's refusal of abdominoperineal resection or associated severe comorbidity. Local control and survival in selected patients (T3N0 with complete response to neoadjuvant therapy) are reported to be similar to those obtained after chemoradiation combined with surgery (TME). Bonnen et al. [50] collected data results from 5 different institutions concerning local full thickness excision or observation after a good response to neoadjuvant chemotherapy. Only two of them, both with incomplete histological response, developed pelvic recurrence at follow-up. They claim a prospective randomised trail comparing T3N0 patients with complete clinical response to radiochemotherapy with those submitted to radical surgery. Criticism can be aimed at this approach because it may leave residual disease in the rectal mesentery and nodes.

More accurate imaging modalities such as the use of endorectal coil MRI and PET should be of help as it can demonstrate sufficient sensitivity in the detection of neoplastic deposits in mesorectum.

Toxicity, Side Effects

Morbidity after neoadjuvant radiochemotherapy is difficult to assess and depends on a lot of variables, i.e., abdominoperineal resection vs. sphincter-saving surgery, type of anastomoses, presence of a diverting stoma, the schedule of RT (dose, fractions), the kind of chemotherapy, the interval between the end of systemic pre-operative therapy and surgery, timing of follow-up, etc. It is reported in literature between 9 and 61%. Comparison of different studies is inconclusive [59].

Generally, with the latest protocols of radiochemotherapy, there does not seem to be a significant increase in morbidity; some Authors report a tendency towards higher rates of infections, anastomotic failure or stricture, but without conclusive data. Pre-operative RT may inhibit healing and contribute to wound complications including delayed wound healing (>1 month), and wound infection requiring drainage or debridement or reoperation in about 40% of cases of patients that undergo APR. Surgeons especially fear anastomotic leakage and pelvic abscess, the leakage incidence rate ranged from 2 to 24% in the literature [60–62].

Pelvic drainage and the use of a defunctioning stoma were significantly associated with a lower anastomotic failure rate. Certainly a protective ileostomy does not influence the incidence rate of leakage of anastomosis but reduces the severity of complications [63].

There is no definitive answer to the influence of RT regarding functional results after conservative surgery. Adequate shielding of the anal sphincter is recommended. Poor functional results (faecal incontinence, more than four daily stools) are associated especially with low anastomosis, not with RT [64].

Neoadjuvant radiochemotherapy adversely affects the functional outcome after total mesorectal excision. There is manometric evidence of a significant decrease of mean resting pressure and mean resting vector volume, as compared with surgery only, as chemoradiation causes internal sphincter fibrosis [65].

Radiation can result in a negative effect on sexual

functioning in females and males, with a higher frequency of ejaculation disorders and erectile functioning that worsen over time [66]. Despite a decrease in sexual function and body image in patients that undergo an APR, one year after combined treatment patients exhibit improvement in some important quality of life outcomes [67].

Hyperthermia

The efficacy of hyperthermia in addition to RT or chemoradiotherapy has been validated in resectable and unresectable rectal cancer. Hyperthermia has a synergetic action with both radio- and chemotherapy. Tissutal temperature, to be effective as a cytotoxic agent, must reach 40–45°C and last 30–60 min.

Hyperthermia can be administered over the whole body or restricted to neoplasm using an internal or external generator. In rectal cancer, endocavitary hyperthermia is usually utilised with an internal electrode that acts as a radiofrequency transducer. In the architectural structure of the neoplasm, with such chaotic vascular vessels, there are hypoperfused areas, poorly oxygenated, with low pH, that are less sensitive to radiation but highly exposed to a thermal increase [68].

Hyperthermia determines an increased blood supply with improved tissue oxygenation and oxygen represents the best sensitising agent to radiation. Hyperthermia seems to increase the cellular uptake and conversion in active metabolisis of some chemotherapeutic drugs such as 5-FU [69].

Authors showed a large quantity of necrotic tissue inside neoplasm and a better complete pathologic response in patients treated with neoadjuvant treatment that included hyperthermia [70–73] (Table 5).

Metastatic and Recurrent Rectal Cancer

The role of surgery in patients affected with stage IV rectal cancer is examined. In this stage of the disease cancer has spread to distant locations: liver, lungs, bones or other sites. Should these tumours be resected or should patients be given only palliative care? The purpose of treatment in this case is to improve symptoms through local control of the disease, and increase a patient's chance of cure or prolonged survival. Patients with advanced rectal cancer should be divided into two groups: patients with single site cancer localisation and patients with widespread tumour (majority of cases).

Chemotherapy in metastatic disease: 5-FU with or without leucovorin was the standard treatment for a long time. This regimen with continuous infusion of 5-FU, modulated with leucovorin or methotrexate, induces remission or shrinkage of the cancer in 10–44% of patients and the average patient survives approximately one year from treatment [74–76].

More recently, several newer chemotherapeutic drugs have demonstrated an efficacy in addition or not with 5-FU: DPD (inhibitors of dihydropyrimidine dehydrogenase), irinotecan (CPT-11), inhibitor of thymidylate synthase (Tomudex) and oxaliplatin (in particular in non-responders to 5-FU) [77–84].

When the site of the metastasis is a single organ, such as liver or lung or ovaries, patients may benefit from local treatment directed at that single site of metastasis. Several clinical trials have reported that surgical resection of metastasis offers a chance of cure in 25% of cases, and mortality and morbidity rates in specialised centres are acceptable.

For patients with limited (3 or less) hepatic metastasis, resection may be considered with 5-year survival rates of about 40% [85, 86].

Highly selected patients with limited pulmonary metastases and patients with both hepatic and lung secondaries may be treated surgically with acceptable 5-year survival rates (30%, and 5-year disease-free 55%) [86].

Patients with non-surgical liver disease may benefit from other procedures such as hepatic artery infusion (HAI) of a chemotherapeutic drug. This procedure has the potential advantage of delivering a higher dose of a chemotherapeutic drug directly to liver metastasis while avoiding the side effects of a systemic delivered chemotherapy. A trial of hepatic arterial floxuridine plus systemic 5-FU plus leucovorin was shown to result in improved 2-year disease-

Table 5. Radiotherapy and hyperthermia

Authors	Patients	Hyperthermia	Treatment	RPC (%)
Berdov, Manteshashvili [70]	56	Endocavitary	40 Gy	13 vs. 1.7 (RT)
Ohno et al. [71]	32	Endocavitary	RT\CHT	30.6
You et al. [72]	44	Endocavitary	30–40 Gy	22 vs. 5.3 (RT)
Rau et al. [73]	36	External	40–50 Gy/5-FU+LV	14

RT, radiotherapy; *CHT*, chemotherapy; *5-FU*, 5-fluoruracil; *LV*, leucovorin

free and overall survival (86% vs. 72%, p=0.03) but did not show a significant statistical difference in median survival when compared to systemic chemotherapy alone [87].

Radiofrequency ablation for metastatic liver disease is preferable to cryotherapy and the complication rate is approximately 10% [88].

When carried out appropriately in patients with advanced rectal disease with peritoneal involvement, surgical debulking performed by skilled surgeons plus chemotherapy improves survival compared with chemotherapy alone. Nevertheless, there is an increased mortality rate of about 8% from sepsis or gastrointestinal fistulae. Some Authors reported better median survival after intraperitoneal chemotherapy vs. systemic CHT [89] after surgical debulking.

Palliation for Local Symptoms in Patients

Self-expanding metal stents are useful to avoid a colostomy in selected patients with incurable rectal cancer and a limited life expectancy. The median technical and clinical success rates are 90–100% and 84–94%. A considerable number of patients will require surgical palliation because of failure of stent treatment (stent migration, pain, incontinence, fistulae, reobstruction) and in cases of low rectal cancer, patients might suffer tenesmus [90, 91]. In these cases and when the predominant symptom is rectal bleeding, endoscopic Nd-Yag Laser ablation is particularly indicated. Other indications for laser therapy are rectal obstruction and mucous discharge. It is feasible and has low complication rates; it requires repeated sessions [92].

Recurrent Locally Rectal Cancer

The goal for the treatment of patients with isolated local recurrence should be local tumour control, as this will determine the quality of the remaining life. Negative predictors of poor prognosis in case of recurrence are: elevated CEA level, APR as primary surgery and male sex. Relapse after APR is often unresectable as it occurs in a pattern of diffuse pelvic cancer or laterally situated masses invading the pelvic sidewall. In addition, the smaller anatomical margins in males diminish the chance of curative resection [93]. In resectable rectal cancer recurrence, LAR, Hartmann's procedure or APR are surgical options preferred, in fit patients, where local clearance is possible and expectation of life is reasonably good.

RT alone (50 Gy) or combined with chemotherapy permits salvage surgery in selected cases of patients with isolated pelvic recurrence.

Authors reported good response to multimodality treatment in patients with advanced pelvic recurrence who underwent RT (45 Gy), concomitant infusion of 5-FU and mitomycin C, IORT (10–15 Gy) and surgery. Radical resection rate was 45% and 5-year overall survival 22% [94].

Pelvic exenteration is an option, although controversial, affected by a high morbidity rate (median survival of 20 months) [95].

Conclusions

Important improvements in the treatment of locally advanced rectal cancer have been achieved. In patients with resectable rectal cancer, RT allows better local control, as lower local recurrence rates have been reported. The downstaging and downsizing of neoplasm consequent to radiation therapy should lead to a major number of sphincter-preserving operations. In addition, pre-operative RT has lower toxicity effects *vs.* post-operative radiation.

The concomitant administration of a chemotherapeutic drug has a synergic effect on local control of the disease and improves the overall survival of patients.

In literature numerous studies with interesting results in terms of downstaging, local recurrence and survival are reported but they are heterogeneous and not comparable as Authors reported different total radiation doses, chemotherapeutic drugs administered, interval from neoadjuvant treatment and surgery, stage of disease, etc.

Improvement of technology in imaging studies, and better acknowledgement of the pathological and molecular characters of neoplasms, allow the correct staging of patients after neoadjuvant treatment.

At the moment we still believe that a radical surgical procedure is a reasonable choice in patients with clinical response to neoadjuvant treatment in rectal cancer (yT0N0). Clinical surveillance is acceptable in cases of refusal of any surgical procedure by patients.

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Chemotherapy in Rectal Cancer

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Introduction

Rectal cancer is a social problem. It represents a third of incidences of neoplasias of the whole colon. The higher incidence of local relapses and worse survival compared to tumours occurring in the rest of the colon have affected the therapeutic strategy. Since the Consensus Conference in 1990 it has been recognised that rectal cancer needs a multidisciplinary approach, radiotherapy and chemotherapy being necessary complements of surgery to obtain the best chance of cure in stage II and III disease. The problems encountered in everyday practice in administering combination adjuvant therapy in the operated colon and the success in treating locally advanced rectal lesions with neoadjuvant radiochemotherapy has favoured attempts in treating operable tumours with a pre-operative multidisciplinary approach.

Adjuvant Therapy

The aims of adjuvant treatment of rectal cancer are reduction of local recurrence and distant failure of disease. Until the end of the 1980s there were discordant data on the real efficacy of post-operative treatments in prolonging disease-free and overall survival in colorectal cancer. In 1990 a NIH Consensus Conference [1] was held to revise the results of recent phase III studies [2–4] (Table 1). The Consensus concluded that in rectal cancer post-operative radiochemotherapy treatment as delivered in study GISTG 7175 [2] was to be considered standard adjuvant therapy both in stages II and III. This treatment had resulted in a 20% advantage in survival compared to the no-therapy arm patients. Nevertheless the combined radiotherapy plus methyl-CCNU and 5-fluorouracil (5-FU) approach caused severe acute enteritis and delayed toxicities such as late enteritis and the onset of acute leukaemias. The Consensus Conference therefore recommended the search for new radiotherapy modalities and less toxic and more efficacious chemotherapy regimens. In the last 10 years two studies have demonstrated that the use of methyl CCNU, a leukaemogenic agent, is not necessary, as it does not add efficacy to the 5-FU only scheme. Furthermore, the NCCTG Intergroup Study 86-47-51 demonstrated that 5-FU continuous infusion is more efficacious than a 5-FU bolus scheme in combination with radiotherapy. No differences in local recurrences and survival have been obtained combining 5-FU with folinic acid (FA) low doses, levamisole, FA plus levamisole or bolus 5-FU alone. Up to now, 5-FU bolus or continuous infusion has been the standard

Table 1. Adjuvant rectal phase III studies before 1990

Study	No. patients	Treatment	Advantage	
			DFS	OS
GITSG 7175	227	Control	–	–
		RT	No	No
		5-FU+methyl CCNU	No	No
		5-FU+methyl CCNU+RT	Yes	Yes
NCCTG 79-47-51	204	RT	No	No
		5-FU+methyl CCNU+RT	Yes	Yes
NSABP R01	555	Control	–	–
		RT	No	No
		MOF	Yes	Yes

Table 2. Adjuvant rectal phase III studies after 1990

Study	No. patients	Treatment
GITSG 7180	210	RT+5→FU RT+MF
NCCTG 86-47-51	453	RT+5→FU (bolus) 5-FU→RT+5→FU (infusion)
INT 0114	1696	RT+5→FU RT+5→FU/LEV RT+5→FU/AF RT+5→FU/AF/LEV

chemotherapy in the combined post-operative treatment of rectal cancer (Table 2) [5–7]. Recently, oxaliplatin and irinotecan, two new drugs largely used to treat advanced disease, have obtained positive results in phase III adjuvant treatment trials. In particular, an oxaliplatin-containing regimen (FOLFOX) has allowed at three years of follow up a further 23% reduction in disease-free survival compared to a 5-FU and FA combination (MOSAIC) [8]. This result, the good tolerability of this therapy and the fact that oxaliplatin is a radiosensitiser suggest that a combination of 5-FU, oxaliplatin and radiotherapy might be planned for the high-risk patient.

Pre-Operative Therapy

Locally advanced colorectal cancer poses a difficult problem for surgeons, oncologists and radiotherapists in terms of patient survival and quality of life. In fact, median survival times after palliative resection are about 10 months, during which time the patient is usually invalid. Around 1990, many random clinical studies showed a significant increase in disease-free survival times in patients undergoing radical curative resection when combined with radio- and chemotherapy [2, 3]. It has been more difficult to demonstrate such results in patients with locally advanced colorectal cancer, as the definitions of resectability and extension of disease are not uniform and may involve neighbouring organs. In addition, there are also different prognoses among primary tumours and relapses, parameters that are not always indicated in various reports, which explains the heterogeneity present in the literature.

Given that the surgeon has a high probability of leaving residual disease in advanced cases of colorectal cancer, pre-operative radiotherapy has become a standard therapeutic approach. This treatment reduces the bulk of the tumour mass and increases the possibility of radical resection even in large lesions, allowing for conservative surgical intervention up to the sphincter. Pre-operative radiotherapy uses doses of at least 4500 cGy and is given four to six weeks before surgical intervention to permit optimal downstaging [9]. The clinical efficiency of pre-operative radiotherapy for advanced colorectal cancer has been demonstrated in multiple reports with a frequency of resectability between 40 and 88% [10–12].

As five-year survival rates are poor (14–28%) and increase only in cases of complete resection (29–43%), pre-operative radiotherapy has been combined with other therapeutic strategies. The use of chemotherapy alongside pre-operative radiotherapy has been proposed in an attempt to increase the possibility of resection and to decrease the dispersion of tumour cells during surgical intervention. Pre-operative systemic treatments may also favour the eradication of circulating neoplastic cells. Such treatments also avoid the problem of the impossibility of carrying out radiochemotherapy when post-operative complications occur. Based on the experience reported by Moertel et al. [13] in patients with recurrent or non-resectable gastrointestinal carcinoma and by Petrelli et al. and Erlichman et al. [14, 15] in metastatic colorectal carcinoma, the use of combined chemotherapy involving 5-FU has been proposed for treatment of patients with locally advanced colorectal carcinoma.

5-FU is an inhibitor of thymidylate synthase and its antiproliferative effect is primarily the inhibition of DNA synthesis. The mode of action of 5-FU together with its ability to render cells more sensitive to radiation [16, 17], demonstrated both *in vitro* and *in vivo*, make this drug highly appropriate for combined chemoradiotherapy. Minsky et al. [18] reported the effects of combined radiochemotherapy in 52 patients who received the same dose of pre-operative radiotherapy (5040 cGy). These patients were subjected to either radiotherapy alone (11 non-resectable/21 resectable cases) or radiotherapy with intravenous 5-FU and folinic acid (20 non-resectable cases). Patients with non-resectable disease who received combined radiochemotherapy showed the highest frequency of response (20 *vs.* 6%) and a lower frequency of positive lymph nodes (30 *vs.* 53%) with respect to those treated with chemotherapy alone. Moreover, in patients with non-resectable disease the frequency of resectability was higher than in patients who received 5-FU and folinic acid with respect to those who were not given chemotherapy (90 *vs.* 64%). In order to obtain a systemic effect and to potentially lower the risk of distant localisation, it was found necessary to continue chemotherapy even after surgical intervention.

Chan et al. [19] reported data of 46 patients treated with pre-operative pelvic radiation (4000 cGy in

20 fractions in 4 weeks), 5-FU infusion (20 mg/m^2, days 1–4 and 15–18) and mitomycin C (8 mg/m^2, day 1). This was followed by surgery 6–8 weeks later. Thirty patients had tethered tumours and 16 patients had fixed tumours. After pre-operative chemoradiation, 41 patients (89%) underwent curative resection. Two patients (4%) had no residual tumour found (T0N0M0); 7 patients (15%) had nodal metastases. The 2-year survival was 73%. The 2-year local relapse rate was 16%. In this study the difference in local relapse between patients with fixed carcinoma *vs.* tethered tumours (38 *vs.* 10%) was statistically significant (p=0.0036). The 2-year distant failure rate was 41%, and the rates were similar for both tethered and fixed carcinomas.

It was recently hypothesised that continuous infusion of 5-FU may have advantages with respect to intravenous therapy in various gastrointestinal tumours with less side effects [20]. Under this supposition, Rich et al. [21] treated 37 patients having locally advanced colorectal carcinoma with 5-FU (i.c. 250 mg/m^2/day) and cisplatin (4 mg/m^2/day) for the entire duration of radiotherapy and reported a three-year survival rate of 82%. The three-year survival rate was up to 62% for patients treated with radiotherapy alone.

Chen et al. in 1994 [22] reported data of 31 patients with fixed rectal cancers (stage ≥cT3) treated with concomitant pre-operative chemotherapy and high-dose radiation in an effort to improve resectability. Three (10%) patients had partially fixed low rectal cancers, 24 (77%) patients had fixed tumours and 4 (13%) had advanced fixation with pelvic sidewall invasion. Radiation was delivered to the whole pelvis using shaped anterior and posterior and lateral fields to 45 Gy followed by a boost to the tumour. Median total radiation dose was 55.8 Gy. Chemotherapy consisted of low-dose continuous infusion of 5-FU (200-300 mg/m^2/day) for the duration of radiation treatment. All 31 patients underwent surgical resection of tumour 6–8 weeks following treatment. Twenty-three (74%) of the tumours were clinically downstaged following pre-operative treatment. Of 24 fixed cancers, 11 (46%) became mobile, 6 (25%) became partially fixed and 7 remained fixed. Of the four tumours with advanced fixation, two (50%) became mobile and two 2 (50%) no longer had tumour extension to the pelvic sidewall. Two of the three initially partially fixed cancers became mobile and one remained partially fixed. Following surgery, the pathologic postradiation T-stages were as follows: T0, 10%; T1, 0%; T2, 32%; T3, 42%; and T4, 16%. Seven patients (23%) were also node-positive (T0-2: 2, T3: 4, T4: 1) and 2 patients (6%) had liver metastases at surgery. Pre-operative chemoradiation was well tolerated. Five patients (16%) developed local recurrence of disease (T0–2: 0/13, T3: 1/13 and T4: 4/5). The 3-year survival was 68%. In this study the concomitant pre-operative chemoradiation using low-dose continuous infusional 5-FU for advanced rectal cancer was found to be safe, with acceptable morbidity. This approach was associated with considerable clinical and pathologic downstaging of cancer. Tumour resectability was improved with potential for improved local control of disease and survival.

In the last few years the demonstration of the efficacy of new effective drugs (oxaliplatin, irinotecan, capecitabine, etc) in the metastatic setting has prompted researchers to introduce these chemotherapeutics in the pre-operative combined treatment. Up to now the association of oxaliplatin with 5-FU has particularly been developed.

Oxaliplatin has been recently demonstrated to have activity against colorectal carcinoma with a response of about 20% when given alone. Some reports have also demonstrated an increase in the antitumour activity of oxaliplatin when given in association with 5-FU [23, 24]. This has been shown both *in vitro* and *in vivo* with response rates of about 50% in patients with advanced colorectal carcinoma. Because oxaliplatin is an analogue of cisplatin it can be hypothesised that the former may also render cells more sensitive to radiotherapy, even though such an effect has not yet been documented [25].

In the phase II Lyon R0-04 study [26], 40 operable patients were treated with two cycles of chemotherapy given in weeks 1 and 5, with 130 mg/m^2 oxaliplatin on day 1 followed by 5-day continuous infusion of 5-FU 350 mg/m^2 and L-folinic acid 100 mg/m^2 synchronously with a three-field technique radiotherapy (total dose of 50 Gy over 5 weeks with a concomitant boost approach). Surgery was planned 5 weeks later. An objective clinical response was seen in 30 patients (75%). Sphincter-saving surgery was possible in 26 patients. No post-operative deaths occurred. In 6 cases the operative specimen was sterilised (15%) and in 12 cases (30%) only a few residual cells were detected. Such a combined pre-operative chemoradiotherapy and oxaliplatin-containing regimen was well tolerated with no increase in surgical toxicity.

Aschele et al. [27] have conducted a phase I study weekly oxaliplatin and 5-FU continuous infusion with concomitant radiotherapy. A dose of oxaliplatin 60 mg/mq/week has been found to be well tolerated. Our group [28] have reported the results of a series of 30 stage II–III rectal cancer patients treated with a pre-operative radiotherapy, chemotherapy plus regional hyperthermia strategy (Fig. 1). Twenty-two patients were stage T3N0, 4 patients were T3N1, 3 were T4N0 and 1 was T4N1. In a pretreatment surgical evaluation 8 patients (26%) were considered suit-

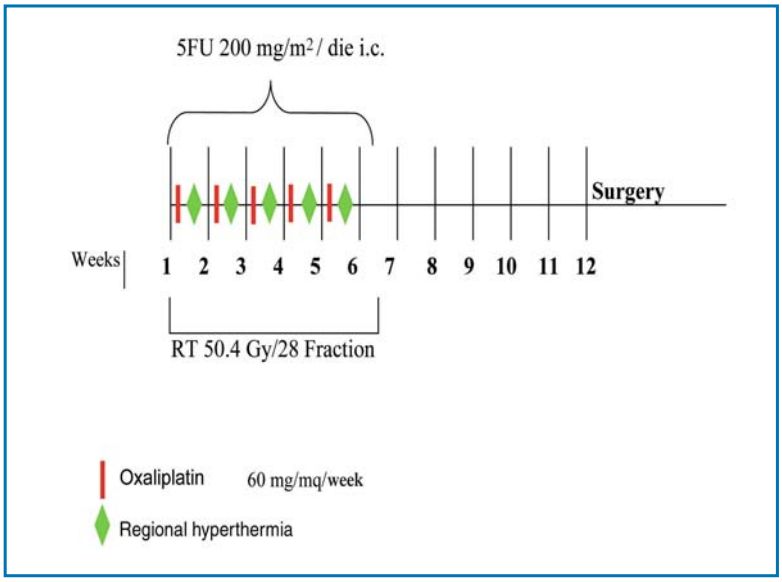

Fig. 1. Pre-operative combination treatment according to [28]

able candidates for sphincter conservation. Treatment consisted in radiotherapy at a median dose of 54 Gy (range 50.4–60 Gy) with daily doses of 1.8–2 Gy and chemotherapy with 5-FU continuous infusion 200 mg/mq/day for the duration of radiation and oxaliplatin 60 mg/mq once a week for 6 times. Regional hyperthermia was carried out once a week prior to radiotherapy for the first 4 weeks. Surgical treatment was carried out 4–6 weeks after the completion of the trimodality treatment. All the patients had resection of the tumour except one who refused surgical treatment. Twenty-six patients (86.6%) underwent conservative surgery. Pathological evaluation revealed downstaging in 66% cases. A complete pathological response (pCR) was obtained in 12 (40%) of pts. One patient had a pCR of the rectal lesion with surgical evidence of liver metastatic involvement. No patient stopped treatment because of toxicity. The conclusion of this study was that trimodality pre-operative treatment for rectal carcinoma was well tolerated and seemed to increase the rate of sphincter conservation.

Carraro et al. [29] reported data of 22 patients with T3–T4 unresectable rectal cancer treated with oxaliplatin 25 mg/mq/day in 30-min infusions, followed by bolus LV 20 mg/mq/day and bolus 5-FU 375 mg/mq/day. All drugs were given on 4 days during weeks 1 and 5 of a standard radiotherapy cycle (50.4 Gy). A single oxaliplatin dose (50 mg/mq) was also given on the third week of radiotherapy. A cycle of oxaliplatin with 5-FU+LV was administered 4 weeks after chemoradiotherapy, with surgery planned 4 weeks later. Of 22 patients, 16 underwent surgery (without serious surgical complications); 12/16 had a complete resection (5/12 had sphincter preservation). Pathologic examination revealed 3/12 complete remissions, 2/12 minimal microscopic residual disease, 2/12 T2N0, 1/12 T3N0 and 4/12 positive nodes; 4/16 had unresectable disease. Median follow-up was 15 months (range: 3.0–43.4 months), median time to progression was 15.7 months (CI 95%, 0, 31.7) and median overall survival was 19.5 months (CI 95%, 18.0, 21). This study confirmed the feasibility of treatment with low-dose, 30-min daily oxaliplatin infusion.

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR), which is converted to 5-FU. Capecitabine plus radiotherapy has the potential to replace bolus or continuous infusion 5-FU with radiation as the standard treatment for rectal cancer. Therefore it appears to simplify chemoradiation and is highly appealing to patients [30].

Kim et al. [31] conducted a study to check the efficacy and toxicity of capecitabine (a new orally administered fluoropyrimidine carbamate) in locally advanced rectal cancer. They treated 45 patients with locally advanced rectal cancer (cT3/T4 or N+) with pre-operative chemoradiation. Radiation of 45 Gy/25 fractions was delivered to the pelvis, followed by a 5.4 Gy/3 fractions boost to the primary tumour. Chemotherapy was administered concurrently with radiotherapy and consisted of 2 cycles of 14-day oral capecitabine (1650 mg/mq/day) and leucovorin (20 mg/mq/day), each of which was followed by a 7-day rest period. Surgery was performed 6 weeks after the completion of chemoradiation. Thirty-eight patients received definitive surgery. Primary tumour and node downstaging occurred in 63% and 90% of

patients, respectively. The overall downstaging rate, including both primary tumour and nodes, was 84%. A pathologic complete response was achieved in 31% of patients. Twenty-one patients had tumours located initially 5 cm or less from the anal verge; among the 18 treated with surgery, 72% received sphincter-preserving surgery. No Grade 3 or 4 haematologic toxicities developed. These preliminary results suggested that pre-operative chemoradiation with capecitabine was a safe, well tolerated and effective neoadjuvant treatment modality for locally advanced rectal cancer. In addition, this pre-operative treatment showed a considerable downstaging effect on the tumour and could increase the possibility of sphincter preservation in distal rectal cancer.

Also Rodel et al. [32] conducted a study to establish the feasibility and efficacy of pre-operative radiotherapy with concurrent capecitabine and oxaliplatin in patients with rectal cancer. They treated 32 patients with locally advanced (T3/T4) or low-lying rectal cancer who received pre-operative RT (total dose, 50.4 Gy). Capecitabine was administered concurrently at 825 mg/m^2 bid on days 1–14 and 22–35, with oxaliplatin starting at 50 mg/m^2 on days 1, 8, 22 and 29 with planned escalation steps of 10 mg/m^2. End-points of the phase II study included downstaging, histopathologic tumour regression, resectability of T4 disease and sphincter preservation in patients with low-lying tumours. These Authors found that grade 3 gastrointestinal toxicity observed in two of six patients treated with 60 mg/m^2 of oxaliplatin was dose-limiting. Thus, 50 mg/m^2 was the recommended dose for the phase II study. T-category downstaging was achieved in 17 (55%) of 31 operated patients, and 68% of patients had negative lymph nodes. Pathologic complete response was found in 19% of the resected specimens. Radical surgery with free margins could be performed in 79% of patients with T4 disease, and 36% of patients with tumours ≤2 cm from the dentate line had sphincter-saving surgery.

The pre-operative strategy has become an appealing possibility of treatment as it has demonstrated a good percentage of downstaging and sphincter-saving operations and good tolerability. Only recently however a phase III study has compared patients with clinical stage T3 or T4 or node positive disease receiving a pre-operative treatment to patients randomly assigned to post-operative chemoradiotherapy. Four hundred and twenty-one patients were randomly assigned to receive pre-operative chemoradiotherapy and 402 patients to receive post-operative chemoradiotherapy. The overall five-year survival rates were 76 and 74%, respectively (p=0.80). The five-year cumulative incidence of local relapse was 6% for patients assigned to pre-operative chemoradiotherapy and 13% in the post-operative-treatment group (p=0.006). Grade 3 or 4 acute toxic effects occurred in 27% of the patients in the pre-operative treatment group, as compared with 40% of the patients in the post-operative treatment group (p=0.001); the corresponding rates of long-term toxic effects were 14 and 24%, respectively (p=0.01) [33]. Even though no difference in overall survival was detected, pre-operative chemoradiotherapy was associated with improved local control and reduced toxicity.

Pre-operative therapy therefore constitutes an alternative to surgery as the primary treatment of high-risk rectal cancer patients. The choice between the two strategies has to take into account the patient's preference and the possibility of administering the pre-operative therapy in a highly experienced multidisciplinary team.

The challenge of the future will be the selection of patients on the basis of biological prognostic factors and the choice of the best chemotherapy regimen according to predictive molecular markers. The other direction taken in research in the neoadjuvant setting is to assess new biological therapies able to selectively target pathways that are critical for tumour growth and development, like angiogenesis [34].

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Modern Aspects of Radiation Oncology for Rectal Cancer

Mario Romano, Antonio B. Porcaro

Introduction

Rectal cancer (RC) accounts for about 30% of all large bowel tumours and is effectively treated by radical surgery, which may also preserve anorectal function when tumours are small, exophytic, mobile and located in the proximal rectum. As stated by the National Institutes of Health Consensus Conference in the United States in 1990 [1], combined treatments including radical surgery and radiation therapy with or without chemotherapy may improve both local control as well as survival when the disease is staged as locally advanced (stages II–III RC), is located to the distal rectum, has poor mobility or deep mucosal ulceration with circumferential bowel wall infiltration and lymph node involvement. Recurrence rates after surgical treatment of RC range from less than 5% to more than 30% and they are probably related to the surgeon's experience and skills, patient selection and different definitions of local failure. A modern concept for the surgical oncologist is the importance of a sharp dissection of the entire mesorectum in patients with potentially curable middle to lower RC, as suggested by Heald [2], who has performed this kind of surgery without any adjuvant treatment in a series of 115 patients reporting, at a mean follow-up of 4.2 years, very low recurrences which were only detected in the pelvis (2.6%) and not at the anastomosis. Circumferential margin is an important factor determining recurrence during potentially curative surgery and it may be predicted by magnetic resonance imaging (MRI) findings while assessing the mesorectal fascia. According to these points, radiation therapy may probably be omitted when surgery without adjuvant treatments is performed by teams who report less than 5% local recurrence rates at five years. On the other hand, a meta-analysis of all randomised trials showed that neoadjuvant are more effective than adjuvant treatments for both reducing local failure rates as well as improving cancer-specific survival [3]. The Dutch trial [4] randomised patients with clinically resectable RC to surgery alone by total mesorectal excision (TME), or short-course radiation followed by TME. In this trial the TME procedures and the pathological analysis of the specimens were standardised to limit the bias due to surgical expertise. While there were no significant differences in overall survivals, local recurrence rates were decreased in the group who received neoadjuvant treatment (12% *vs.* 6% at five years) [5]. Based on the results of the recently completed German Trial [6], patients with T3 and/or N1–2 RC should receive pre-operative combined modality therapy and undergo TME with adequate nodal dissection. The potential advantages of neoadjuvant therapy include earlier onset, increased tumour radio sensibility, decreased radiation complications, decreased local recurrence rates due to tumour seeding during the surgical procedure, and, probably, increased feasibility of performing sphincter-sparing surgery. The primary disadvantages of neoadjuvant therapy are the absence of a pretreatment pathological classification with a risk of overtreating small tumours as well as the risk of understaging lymph node status. Lymph node staging in patients who undergo pre-operative radiotherapy alone or in combination with chemotherapy should be interpreted with caution because the clinical relevance of the number of nodes involved and the pathologic stage are not completely evaluated by clinical studies. For example, a large study reported that T3N0 RC patients, who had undergone surgery combined with post-operative radio and/or chemotherapy, had a poor prognosis if few lymph nodes had been evaluated by the pathologist [7, 8]. MRI advances have improved the selection of patients with stage T2–T3 disease, thus reducing overtreatment of pre-operative radio- and chemotherapy. Advanced MRI with particular contrast medium will improve accuracy in staging the lymph node metastases as well as patient pre-operative selection for aggressive chemoradiotherapy regimens. As RC represents not a uniform entity but a wide spectrum of diseases, it is extremely important to classify and stage RC patients correctly because the application of radiotherapy principles requires information including concerning tumour biology,

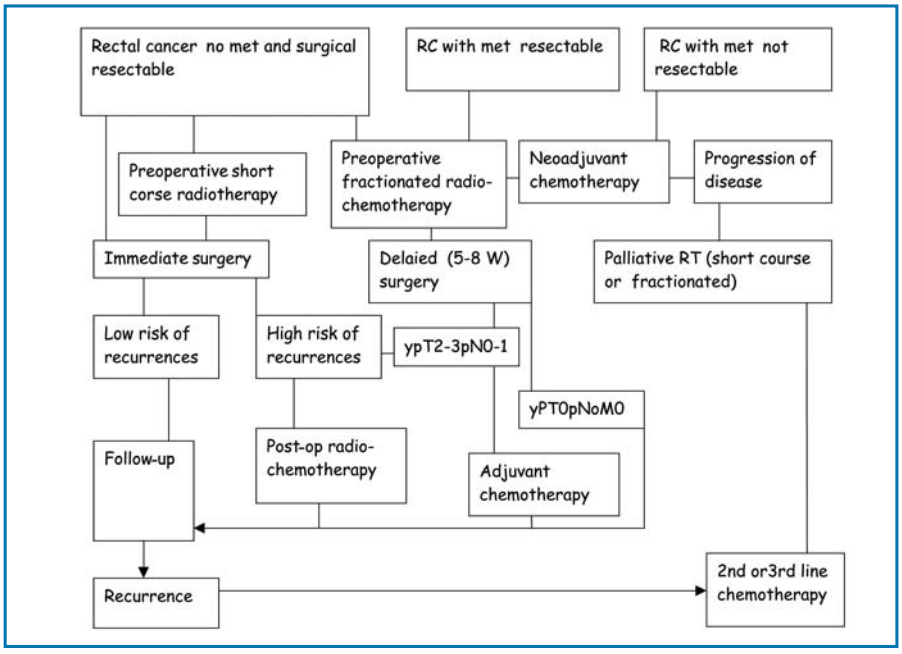

Fig. 1. RC radiation therapy and patient selection

surgical procedures and expertise, anatomy of the pelvis, and RC failure patterns. In conclusion, we think that the modern approach of radiation oncology is to select the best patient for the best treatment. After this overview and as depicted in Fig. 1, we will briefly describe RC radiation therapy dealing with patient selection and protocols as performed at our institution.

Post-Operative Radiation Therapy

In our institution, we rarely perform post-operative radiation therapy, which is frequently associated with 5-fluorouracil (5-FU)-based chemotherapy and is delivered when the surgical specimen of a good patient selected for exclusive surgery shows risks of local recurrence such as incomplete tumour resection as well as nodal disease involvement. Post-operative radiotherapy has shown the advantage of being selectively delivered in patients at high risk of local recurrence as well as the disadvantage of the increased risk of radiation damage of the small bowel loops which may be fixated to the pelvis as a result of the surgical procedure. The risk of small bowel injury has decreased with the advent of a 3D planning system, dietary care and not exceeding the limit dose of 50–54 Gy. Complications of pelvic radiation therapy are related to the radiation field volume, surgical procedure, overall treatment time, fraction size, radiation energy, total dose and technique [9]. Generally, successful treatment of RC depends on large irradiation fields whose arrangement depends on the location of the primary tumour, surgical procedure (low anterior vs. abdominal perineal resection) and volume of the small bowel. Small bowel radiation induced complications are directly proportional to their volume and may be reduced by using contrast media in defining the radiation fields. Gallagher et al. [10] determined the volume, distribution and mobility of small bowel in the pelvis by using different techniques. There was a significant average small bowel volume decrease when patients, compared with the supine position, were treated in the prone position with compression of the abdominal wall and distension of the bladder. At our institution we use the prone position and a custom-made belly board for selected patients undergoing post-operative radiation therapy [11]. The knowledge of both local and nodal failure patterns is important for planning radiation therapy fields which should include all potentially contaminated retroperitoneal soft tissue. The majority of local failures in cases of APR occur in the posterior pelvis, presacral space, primary tumour site and perineum. The reported risk areas include the internal iliac, presacral and obturator lymph nodes. After an APR, a wire marker should be used to identify the perineal scar for defining the inferior limit of the beams. When the rectum is resected anteriorly, a Foley catheter is inserted into the rectum and retracted inferiorly in order to identify the anorectal junction and define the inferior limit of the beams. The cranial limit of the field is usually L5-S1 interspace; the lateral borders extend 1.5–2 cm lateral to the widest part of the pelvis bones. Posterior fields include the whole sacrum including a 1-cm posterior

margin to allow dose to build up in the presacral area. The anterior border is defined to encompass the internal or internal plus external iliac nodes according to the pathological N stage. When boost doses of radiation are required, the fields are redesigned and 3D treatment planning are performed in order to spare the tissues which are considered not at risk. At present, intensity modulated radiation therapy (IMRT) does not have an established role in post-operative radiation therapy for RC including stages assessed as T3N0N+ and M0R0.

Pre-Operative Radiotherapy

In our department pre-operative radiotherapy is the standard treatment for stage 2–3 rectal RC and, as reported before, an increasing body of data suggests the superiority of pre-operative radiotherapy combined with chemotherapy in terms of local control, disease-free survival and reduction of bowel toxicities. There are two types of pre-operative radiotherapy: fractionated radiotherapy and short course. Short-course pre-operative radiotherapy is delivered one week before surgery in 5 daily fractions of 5 Gy without any chemotherapy. Pre-operative fractioned radiotherapy is delivered in a period longer than 5 weeks (daily doses of 1.8–2 Gy for total doses of 45–50 Gy), usually with a 5-FU schedule, and is followed by surgery which is performed 4–6 weeks after in order to restore the acute damage and as well as to reduce tumour volume. Probably the most important argument in favour of pre-operative radiation therapy is tumour regression, which may improve the likelihood of a successful resection with free margins. The possibilities of preserving the sphincter are increased for regressing tumours arising in the distal rectum. From this point of view, short-course radiation offers low tumour reduction probabilities due to the surgery timing. The choice of treatment is fractionated radiotherapy because it offers a high probability of sphincter preservation. After pre-operative chemo- and radiotherapy, a pathologic complete response rate of 10–25% has been reported as well as a tumour downstaging rate of 40–80% with both improved local control and survival [12, 13]. For this reason, different institutions, including our department, have routinely used some form of dose intensification and the addition of chemotherapeutical agents such as oxaliplatin in order to increase the pathological complete response rate as well as local control and survival. By using a novel, custom-made, modified belly board, we investigated the effects of reduced radiations on the small bowel as well as their effects on volume and median dose. Using a four-field box technique, the mean dose of the small bowel of patients treated on our belly board was significant lower than with the standard technique [14]. We have also investigated the possibility with this bowel device of an escalation of the radiation dose. Between October 1998 and December 2002, 109 patients with primary RC (T3–T4) underwent pre-operative radiochemotherapy plus hyperthermia with escalation of the radiation dose. The median total dose in this series was delivered and escalated as follows: 54 Gy in the first 21 patients, 56 Gy in the second group of 41 patients, 62 Gy in the third group of 22 patients and 64 Gy in the fourth group of 25 patients. The treatment was well tolerated without any significant side effect. Six patients with a clinical complete response refused surgery and were submitted to an intensive surveillance protocol. The pathological complete response rate was 30% and the local recurrence rate was 2%, and also the survival was 76% after mean follow-up of 4 years. Of the 6 patients that refused surgery, 1 patient died from metastatic disease without evidence of local recurrence, while the other 5 patients are still alive without disease. A multivariate analysis showed that radiation doses >60 Gy and tumour length less than 3 cm were related to a higher rate of complete pathological responses. In this experience, dose escalation may have contributed to an increase of the pathological complete response rate and to a better outcome for patients refusing surgery [15]. A valid criticism of this kind of study is that we do not know how applicable the staging system is for patients who have undergone pre-operative radiochemotherapy. Probably, post-treatment pathologic findings represent a composite situation of stage of the tumour and its response to pre-operative therapy and pathological complete responders may simply represent the quota of patients with less aggressive disease and/or with a disease that strongly responds to the treatment. In the future, the use of more precise pre-operative staging systems will allow evaluation of how pre-operative radiochemo-downstaging may impact patient survival. Of much interest is the report of overall long-term results of stage 0 RC following neoadjuvant chemoradiation that compared operative and non-operative treatment [16]. In this report, after radiochemotherapy patients with incomplete clinical response treated by surgery resulting in stage pT0 were compared to patients with complete clinical response not treated with surgery: five-year overall and disease-free survival rates were 88 and 83%, respectively, in the resection group and 100 and 92% in the observation group. The Authors concluded that stage 0 RC disease after radiochemotherapy is associated with excellent long-term results irrespective of surgical resection.

Treatment of Local Recurrences

Local recurrent RC represents a major problem to the surgical oncologist, occurs in 4–5% of patients after apparently curative resection and is resectable in only 15–20% of cases. This type of pelvic tumour causes significant morbidity and accounts for 90% of disease-related deaths within five years. Surgical resection is the initial choice of treatment. The objective, if feasible, is removal of both the tumour and primary nodal drainage with as wide a margin around them as possible. If recurrence occurs in patients not previously treated with radiation therapy, pre-operative radiochemotherapy is highly recommended and it is possible to complete the radiation treatment in case of suboptimal resection of the tumour with intraoperative radiation therapy boost (IORT). Patients who achieve a gross total resection at the time of IORT have a markedly better prognosis than those with residual gross disease. The major IORT-related post-operative complications are leakage from anastomoses, deep pelvic abscesses and peripheral nerve injury causing lower extremity weakness. Other complications including perineal pain, hydronephrosis and bladder perforations are less common [17]. In previously heavily irradiated patients the treatment is mainly palliative with hypofractionated radiation therapy regimens and chemotherapy. The Dutch Hyperthermia group investigated with a randomised trial the effect of additional hyperthermia in recurrent inoperable tumours of the rectum. In this trial 50% of the patients were randomised to standard radiation alone and 50% to combined treatment. The complete response rate was 13% following radiotherapy alone and 19% following combined treatment. This difference was not significant so it did not lead to any definitive conclusion [18]. At our department we have also treated a consecutive series of 44 patients for RC local recurrences with regional hyperthermia plus radiochemotherapy with a good complete pathological response rate in patients not previously irradiated, and a good palliation of symptoms without any relevant toxicity in those previously irradiated for more advanced disease [19].

Conclusions

In conclusion, a wide spectrum of radiation treatment possibilities are available for all clinical presentations of RC natural history. We need to perform a global strategy of appropriate patient selection and combine the different treatment modalities including surgery, radiotherapy, chemotherapy, IORT, hyperthermia and (more recently) immunotherapy. These multimodality and integrated treatment programmes will allow a more conservative treatment in limited disease, better survival and reduction of local recurrence in advanced disease, and good symptom palliation in recurrent or metastatic disease.

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Surgical Therapy of Hepatic Metastases

Alfredo Guglielmi, Silvia Pachera, Andrea Ruzzenente

Introduction

The development of hepatic metastases in patients with rectal cancer represents an unfavourable prognostic element; chances of curing these patients are often limited by the extension of the neoplastic disease.

The rectum, unlike the colon, presents dual venous drainage, which occurs through the mesenterico-portal system and internal iliac veins, leading to the inferior vena cava. This dual venous drainage can explain the different frequency for hepatic metastases in colonic or rectal cancer; the incidence of hepatic metastases from colonic tumours is 56.8% and 45.9% in rectal tumours [1].

Incidence and Natural History of Hepatic Metastases from Rectal Cancer

Rectal cancer represents 39% of all colonic cancer in western countries, and its incidence and mortality is lower only than breast cancer in women and lung cancer in men.

During the natural history of the disease about 50–60% of patients will develop liver metastases: in 20% these are isolated to the liver, whereas 80% are associated with other sites. The identified risk factors for the development of hepatic metastases in rectal cancer are the rectal tumour stage, the presence of microscopic venous invasion and the histotype of primary tumour (Table 1) [2]. Among various histotypes, the mucinous histotype has the highest risk of developing liver metastasis.

Table 1. Extrahepatic disease by site

Site	Frequency (%)
Lungs	32
Peritoneum	20
Lymph nodes	9
Ovaries	7
Adrenal	3
Multiple	29

Hepatic metastases may be divided into synchronous, in 15–20% of patients, and metachronous, in 50% of patients. Metastases are synchronous when they are recognised during the diagnosis of primitive tumour and metachronous when they are diagnosed during follow-up of the primitive tumour. It is possible that microscopic metastases already exist at the time of the diagnosis of the primitive tumour and are not diagnosed at the time of the rectum resection surgery.

These considerations could explain the lack of homogeneity in the literature regarding the time limit to define the synchronous or metachronous metastases. Headrick and Miller [3] proposed a cut-off time of 3 months between the diagnosis of the primitive tumour and the appearance of the metastasis. Within 3 months of rectal cancer diagnosis, the metastasis is defined as synchronous; after 3 months the metastasis is defined as metachronous.

Many studies in the 1970s and the 1980s reported the natural history of patients with liver metastases without any treatment. In these patients survival is very low: 10–20% 3-year survival, with few patients surviving more than 5 years and an extremely variable mean survival, ranging from 3 to 24 months [4].

In these patients survival is related to the extent of the hepatic involvement, with 1-year survival of 60% for patients with single metastasis, 27% for patients with multiple metastases localised to one lobe or to one hepatic segment and 5.7% for patients with massive hepatic involvement. Patients with single metastasis have mean survival of 25 months and a 3-year survival of 20%. The potential resectability of metastases may also affect survival: 1-, 3- and 5-year survival for patients with non-treated but potentially resectable metastases is 77%, 23% and 8%, respectively, whereas for patients with non-resectable metastases it is 15% after 1 year, with no patients surviving more than 3 years [5].

On the contrary, patients submitted to hepatic

resection have good results, with 5-year survival ranging from 26 to 45%, with low surgical morbidity and mortality lower than 3%. Unfortunately, only 10–20% of patients suffering from hepatic metastases from colorectal cancer can be submitted to hepatic resection.

Diagnosis

The pre-operative evaluation of patients with hepatic metastases from rectal cancer must include an accurate staging of the primitive rectal cancer, of the liver metastases (number, site and size of hepatic metastases) and of extra-hepatic disease. The imaging techniques utilised for pre-operative evaluation are: ultrasound, CT, MRI and PET.

Ultrasound examination plays an important role in detecting liver metastases and is able to identify very small lesions within the liver. Sensitivity is good and varies from 86 to 90%, with a specificity higher than 90%. Obesity, presence of intestinal meteorism and liver steatosis can limit the efficacy of the technique. Moreover, subglissonian and posterior metastases, especially smaller than 1 cm, are difficult to detect. Colorectal metastases with ultrasound may be either hyperechoic or hypoechoic, even if in 80% of the cases they are hyperechoic surrounded by a hypoechoic halo. Differentiation from primary tumours or benign lesions is most difficult when lesions are smaller than 1.5 cm. In these cases, for a better characterisation of the lesion and its vascularisation, the use of contrast-enhanced ultrasound may be helpful.

Computed tomography is the most accurate and widely available technique for detecting and characterising liver metastases. Moreover, CT has a primary role in staging rectal cancer. Sensitivity in identification of liver metastases reaches 70–85%, with a specificity of 90%, especially for lesions bigger than 1.5–2 cm. CT sensitivity is lower for small liver subglissonian metastases even though recent multi-slice CT allows identification of hepatic lesions of 0.5 cm in size.

Hepatic metastases from rectal cancer are hypodense without contrast medium; after the contrast medium they are hypodense during the arterial phase; and they are remarkably hypodense in the portal phase in comparison with the surrounding healthy parenchyma (Fig. 1).

Magnetic resonance imaging (MRI) has gained approval in recent years and shows good sensitivity and specificity in the diagnosis of hepatic lesions. Sensitivity varies from 85 to 90%; specificity is higher than CT, up to 95%. MRI in liver metastases is useful in the characterisation of the lesion (differential diagnosis between primary and secondary liver tumours) and in definition of the precise relationship between lesions and vascular structures. The use of paramagnetic contrast agent (gadolinium-DTPA) or iron oxide-based superparamagnetic contrast media (SPIO) allows an increase in the sensitivity and specificity of the methodology, even though it is still in an assessment phase.

Positron emission tomography (PET) in liver metastases has high sensitivity and high specificity, 92–100% and 85–100% respectively. Sensitivity in small lesions (<1 cm) is limited and it does not show relevant improvements of its diagnostic ability in comparison with CT and MRI.

The diagnostic role of monoclonal antibodies conjugated with radioactive compounds is still not conclusive. An advantage of their application has still not been demonstrated, and moreover, nowadays high costs are not justified.

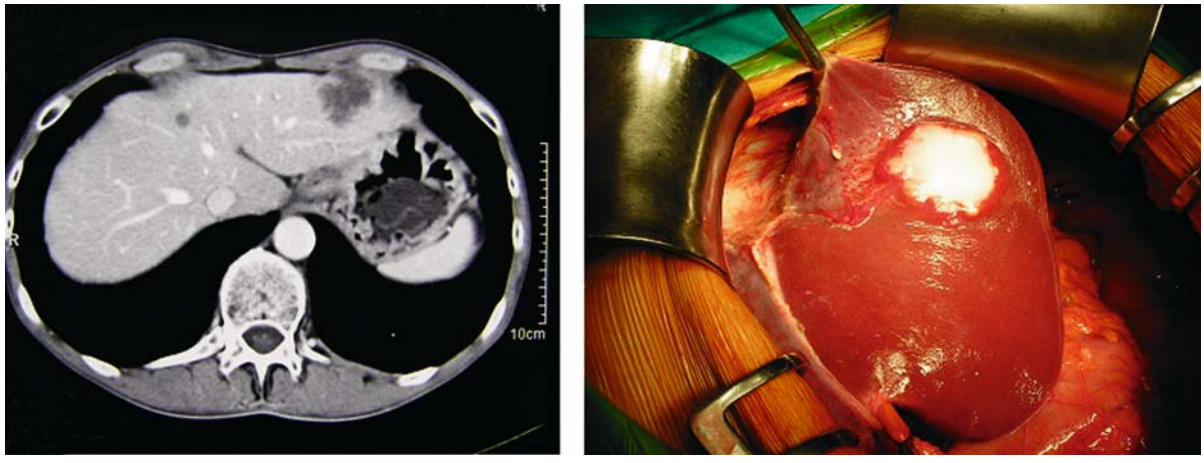

Fig. 1. CT and surgical field of a liver metastases of rectal carcinoma. The lesions are located on the left lobe

Table 2. Predictor of recurrence after hepatic resection for metastatic colorectal cancer

Study	Patient age	Primary stage	Metastases					Chemo	Surgical margin	CEA
			Synchronous	Size	Number	Bilobar	Satellite			
Foster [6]	–	N	N	Y	Y	–	–	–	–	–
Adson et al. [7]	–	N	N	N	N	N	–	–	–	–
Fortner et al. [8]	N	Y	–	N	N	–	–	N	–	N
Butler et al. [9]	N	Y	N	N	N	–	–	N	N	–
Nordlinger et al. [10]	–	–	–	N	N	–	–	–	–	–
Cobourn et al. [11]	–	N	N	–	Y	–	N	–	–	–
Hughes et al. [4]	–	Y	Y	Y	Y	Y	–	Y	Y	Y
Schlag et al. [12]	–	–	Y	–	–	–	–	–	–	–
Doci et al. [13]	N	Y	N	N	N	N	–	–	–	N
Younes et al. [14]	–	N	N	Y	Y	–	–	–	–	Y
Scheele et al. [15]	N	Y	Y	N	N	N	Y	–	Y	–
Rosen et al. [16]	–	N	N	N	N	–	Y	–	N	–
Cady et al. [17]	N	N	N	N	Y	–	–	–	Y	Y
Fong et al. [18]	N	Y	Y	Y	Y	Y	–	Y	Y	Y
Gayowsky et al. [19]	Y	Y	N	N	Y	Y	–	–	Y	–
Nordlinger et al. [20]	Y	Y	Y	Y	Y	N	–	–	Y	Y
Scheele et al. [21]	N	Y	Y	Y	N	N	Y	–	Y	Y
Fong et al. [22]	N	Y	Y	Y	Y	Y	–	–	Y	Y
Minagawa et al. [23]	N	Y	N	N	Y	N	–	–	N	Y
Scheele et al. [24]	Y	Y	Y	Y	Y	N	N	Y	N	Y

Intraoperative diagnosis is based on *intraoperative ultrasound* and on *diagnostic laparoscopy*. The sensitivity of intraoperative ultrasound is very high, reaching 98–100%. It allows identification of small metastases of 0.5 cm in size and defines the relationship between lesion, vessels and biliary structures. For these reasons it must be considered as a routine investigation to be performed in all patients with hepatic metastases, which is able to modify planned surgical intervention in more than 30% of patients.

Laparoscopy, which is not routinely used in the pre-operative evaluation of the advanced disease, allows a reliable study of the peritoneal and pelvic diffusion of the primitive rectal cancer. The combined use of laparoscopic ultrasound (LIOUS) also allows identification of the presence of small metastases, modifying the initial surgical project in 20–30% of cases.

Prognostic Factors after Hepatic Resection

In patients who underwent a radical resection of both rectal cancer and liver metastases, many prognostic factors were identified and proved to be important in predicting survival (Table 2). All prognostic factors that were proposed require as a necessary condition that both rectal and hepatic resection must be radical (R0) [25]. This condition is associated with a 5-year survival value which may exceed 40%, whereas in the

case of non-radical resections, with a microscopic (R1) or macroscopic (R2) residual disease, survival is substantially comparable to palliative therapies, with a 5-year survival of 0–3% [22].

In 90% of patients, mortality after hepatic curative resection is determined by disease recurrence both at a hepatic and extra-hepatic level. The prognostic factors may be grouped into 3 categories: the patient's, the primitive tumour's and the hepatic metastases' characteristics.

Patient's Features

Gender does not affect the prognosis, whereas *age* may affect operative risk and the patient's selection, without influencing the long-term survival of patients exceeding the immediate post-operative period [23, 26].

Primitive Tumour Features

The *stage* of the primitive tumour is an important prognostic factor. Dukes C stage is associated with worse prognosis, with a 5-year survival in 25% of patients compared with 40% of patients with Dukes stage A and B. Scheele et al. [5, 24] emphasise that the stage of rectal cancer has a prognostic value only in the case of the presence of hepatic synchronous metastasis.

Rectal localisation in comparison to colonic seems to represents an unfavourable prognostic factor, even though this observation is not shared by all Authors in the literature [22, 24, 27].

Hepatic Metastases Features

The *presence of symptoms* caused by secondary metastases and alteration of hepatic function represent variables correlated with a worse prognosis after an R0 hepatic resection.

Carcinoembryonic antigen (CEA) pre-operative level may be considered as an aggressive behaviour of the tumour with a higher risk of recurrence, both in the primitive rectal tumour and in the secondary hepatic metastases. Nordlinger reports a 5-year survival of 30% in patients with a CEA pre-operative value lower than 5 ng/ml and 18% in patients having a value higher than 30 ng/dl [28].

It is still under discussion whether there is a significant difference in terms of survival between the *synchronous and metachronous* metastases. Some Authors report a higher survival rate among patients with metachronous metastases, but only if it appears later than 12 months after resection of primary tumour. Hughes et al. [4] report a 5-year survival rate of 42% in patients with a disease-free period longer than one year, and 24% for patients with diagnosis of liver metastases within 12 months after primary rectal surgery. More recently, other Authors showed no differences in terms of survival between patients submitted to radical liver resection with synchronous or metachronous metastases [5].

Size and number represent considerable prognosis factors. The number of metastases significantly influences survival and the best results in terms of survival have been observed in patients with less than 4 metastases. The number of metastases influence the likelihood of removing all lesions, more so if lesions are localised in both lobes. A higher rate of radical resections should explain the better results in patients with less than 4 nodules reported in the literature [29]. Fong et al. [18] report a 5-year survival of 47% in patients with single hepatic metastasis, 31% in patients with 2 or 3 metastases and 24% in patients with more than 4 metastases. Nowadays more than 4 metastases does not represent a contraindication to hepatic resection, as long as a radical resection can be performed.

Satellite nodules are found in 14–24% of patients and must be distinct from multifocal hepatic metastases [31]. Satellite nodules develop through local diffusion via the portal vein system and indicate an aggressive behaviour of the tumour, characterised by an early vascular invasion. Satellite nodules are defined as the presence of two or more nodules located less than 2 cm from the main lesion and with a diameter lower than 50% of the primitive hepatic metastasis.

Satellite nodules increase the risk of developing metachronous lung metastases that in these patients are twofold higher than in patients without satellite nodules. Five-year survival is 11–17% for patients with satellite nodules and 30–47% for patients without satellite nodules [15].

The *extension of the hepatic involvement* represents an important prognostic element, even if the techniques used to measure the hepatic parenchyma have not been standardised. Five-year survival is 22% for patients with hepatic replacement less than 25% of the whole liver, compared with 9% of survival for patients with a hepatic replacement of 25–50% of the liver.

Lymph node involvement of the hepatic hilum represents one of the most important elements affecting the prognosis after radical resection. Nowadays it is clear that involvement of hilar lymph nodes, through the lymphatic drainage coming from the liver, is a sign of tumour progression in patients with liver metastases. Lymph node involvement of the

hepatic hilum, of the hepatoduodenal ligament and of the coeliac tripod represents an element for an unfavourable prognosis. Laurent and Rullier [30] report lymph node involvement in 15% of cases, associated with 0% 5-year survival, after radical resection and hilar lymphadenectomy. The 3- and 5-year survivals were 0% and 3% for patients with N+ lymph nodes at the hepatoduodenal ligament, in comparison with 48 and 22% in patients with N– [31]. Nakamura et al. [32] proposed an extended lymphadenectomy of the hepatic pedicle in selected patients. This Author performed this procedure without an increase in morbidity. Lymph node involvement was observed in 14% of patients and 5-year survival with N+ reaching 40%, even if they underwent reiterated resections due to hepatic recurrence. These data support the theory that an aggressive surgical attitude, in carefully selected patients, may lead to good results in terms of survival, even though it is not yet a standardised procedure.

Extra-hepatic metastases represent the most negative prognostic element and contraindicate hepatic resection. It is important to distinguish distant metastasis from metastases of structures adjacent to the liver, such as diaphragm, retrohepatic vena cava, vascular structures of the hepatic hilum, extra-hepatic biliary tract, omentum, right colonic flexure, stomach and transverse colon. In these situations radical resection of hepatic metastases and of the infiltrated organs may, in rare and selected cases, have good results, with a 5-year survival of 33%.

Isolated lung metastases are discovered in only 2% of patients, whereas associations between liver and lung metastases are observed in 25% of patients. In carefully selected cases, resection of both lung and liver metastases has acceptable results: Headrick and Miller [3] report combined resection of hepatic and lung metastases with a morbidity of 12% and a 5-year survival of 30%. The presence of metastatic lung lymph nodes and high levels of CEA are associated with a reduction of the survival. In 2003, Elias and Ouellet [33] reports a 5-year survival of 33% for patients who underwent hepatic resection, hepatic hilum lymphadenectomy and a resection of 1 or 2 lung metastases.

Type of Surgical Resection

Results of anatomic and non-anatomic resection do not seem to be different in terms of survival as long as radical resection is possible. Anatomical resection or major hepatic resection are preferred because of the reduced incidence of non-radical resections [34].

Resection Margins

Many Authors advise a safe margin of healthy tissue larger than 1 cm [4, 28]. More recently, clinical studies showed that the 1 cm limit, determined by Ekberg in 1987 [35], is not so imperative. Survival is significantly worse in patients with positive surgical margins, with no survivors after 5 years. But for patients with negative margins, survival is not different for margins greater or smaller than 1 cm, with 5-year survivals of 43% and 37%, respectively [21]. As a consequence, it seems that nowadays it is feasible to perform, especially in the case of multiple metastases, metastases resections with margins lower than 1 cm, as long as R0 surgical radicality is granted.

Indications and Contraindications in Surgical Therapy

The indications for resection of hepatic metastases are obtained from the analysis of the prognostic elements described above. The pre-operative evaluation of the patient should consider general examinations for abdominal general surgery and evaluation of liver function [36]. In patients with normal liver function, resections of 70–80% of the total hepatic mass can be safely performed. In patients submitted to per-operative chemotherapy or with chronic liver disease, resection should be limited to 50–60% of total liver volume to reduce the risk of post-operative liver failure.

Surgical indications for metachronous metastases are related to the possibility of performing a hepatic radical resection and the absence of extrahepatic metastases.

Synchronous metastases are found in 20–30% of patients; among these only 10–25% are resectable. Surgical management of this group of patients is still controversial and debated.

If both rectal cancer and liver metastases are resectable, two different strategies might be chosen: simultaneous resection both of the rectal cancer and metastases, or resection of the rectal cancer with a delayed hepatic resection. The debate about these different strategies is still underway: many Authors in the literature report high percentages of mortality and complications due to simultaneous resection of colon and liver and advise simultaneous resection only for small metastases that require limited resection; for major hepatic resection they suggest waiting to perform resection at least two months after rectal resection. Nordlinger et al. [20] report a post-operative mortality of 7% in simultaneous resections, in comparison with 2% of delayed resections. Bolton

Table 3. Published results of simultaneous *vs*. staged resection for synchronous colorectal hepatic metastases

Authors	Year	*n*	Type of resection	Morbidity (%)	Mortality (%)
Vogt et al. [42]	1991	36	19 simultaneous	5.2	0
			17 staged	17.6	
Scheele et al. [15]	1991	98	60 simultaneous	n.r.	2
			38 staged		
Elias et al. [39]	1995	53	53 simultaneous	19	0
Jaeck et al. [43]	1996	41	20 simultaneous	20	0
			21 staged	10	
Nordlinger et al. [20]	1996	1008	115 simultaneous	n.r.	7
			893 other		2
Jenkins et al. [44]	1997	46	22 simultaneous	n.r.	n.r.
			24 staged		
Bolton, Fuhrman [37]	2000	165	50 simultaneous	n.r.	12
			115 other		4
Fujita, Takayuki [40]	2000	97	83 simultaneous	58	0
			14 staged		
Lyass et al [45]	2001	112	26 simultaneous	27	0
			86 staged	35	2.3

n.r., not recorded; *other*, staged and metachronous resections

and Fuhrman [37] report a post-operative mortality of 24% in simultaneous resections that require major hepatic resections. Other Authors report that the simultaneous resection of the primitive tumour and hepatic metastases is safe with recent improvements and progress in rectal and hepatic surgery [38]. Elias et al. [39] and Fujita and Takayuki [40] reported an operative mortality near to 0%, and morbidity rates ranging from 19 to 33%. Some Authors suggest a different behaviour according to the site of colonic cancer; a right colon resection may be associated to major hepatic resection while left colon resection should be associated only to minor hepatic resections. Martin and Paty [41] emphasised that the site of the primitive tumour (rectum or colon) and the extent of the hepatic involvement do not represent risk elements for the outcome of the surgical intervention. They stressed the importance of the experience of the surgical team. Post-operative complications and mortality reported by these Authors are comparable with those of the delayed operation (Table 3).

When multiple small (<1–2 cm) metastases are discovered at the time of colonic surgery, some authors suggest waiting at least 3 months before liver resection, with ultrasound monitoring every 4 weeks to monitor tumour progression.

If the rectal tumour is not resectable, the hepatic resection, even if it is technically feasible, is contraindicated, because patients do not have any improvement in survival. When the rectal cancer is resectable with unresectable hepatic metastases, it is advisable to proceed with rectum resective surgery, associated with systemic chemotherapy for hepatic metastases, whether or not associated with locore-

Table 4. Principles of surgery. Criteria for resectability of metastases (NCCN Practice Guidelines in Oncology, 2005 [47])

Liver
- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of noble hepatic function is required
- There should be no unresectable extrahepatic sites of disease
- Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer
- Ablative techniques should be considered in conjunction with resection in unresectable patients

Lung
- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required
- Resectable extrapulmonary metastases do not preclude resection
- The primary tumour must be controlled
- Re-resection can be considered in selected patients

Table 5. Models for multimodality treatment of NCCN Practise Guidelines in Oncology, 2005 [47]

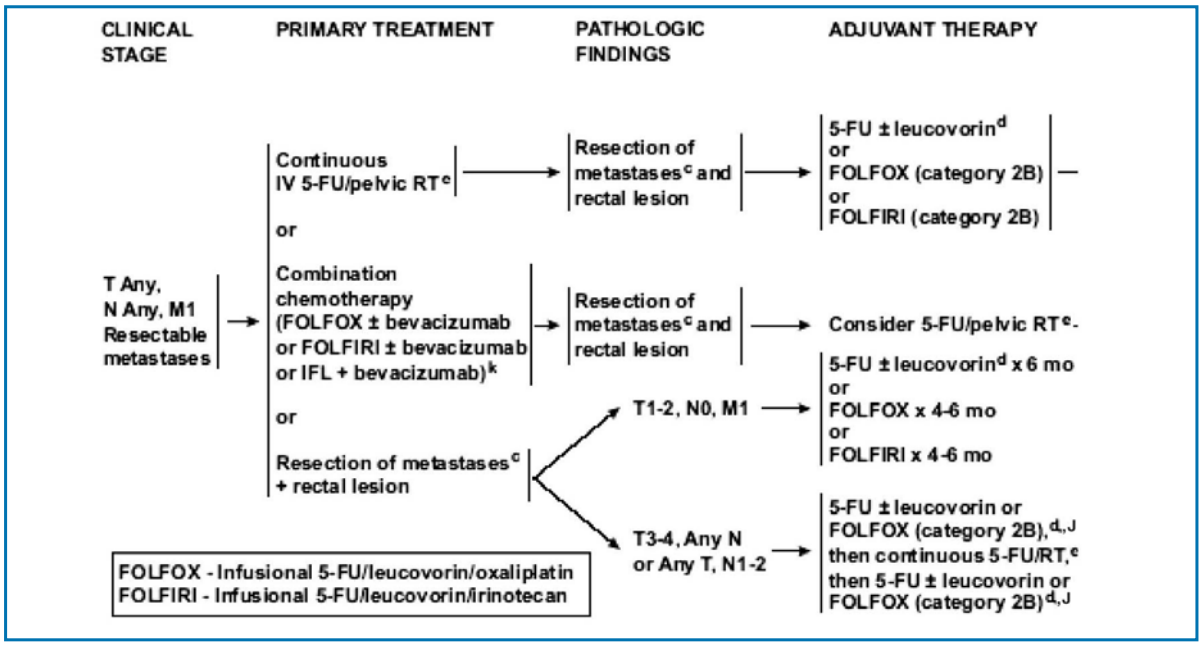

Table 6. Complications after surgical procedures

Type of complication	Frequency (%)
Liver	
Bile leak	3–5
Perihepatic abscesses	1–9
Liver failure	1–5
Post-operative bleeding	1–2
Renal failure	1
Portal thrombosis	1
Infection	
Wound infection	1–6
Sepsis	1–2
General complications	
Pleural effusions	5–8
Pneumonia	2–8
Myocardial infarction	1–5
Gastrointestinal bleeding	1
Deep vein thrombosis	1
Pulmonary embolism	1

gional chemotherapy, or with interstitial therapies. If the primary tumour and the hepatic metastases cannot be resected, there is no suggestion to perform surgery, but only supporting palliative medical therapy is advised. In patients with hepatic and lung metastases, associated treatment is advisable in patients suffering from resectable hepatic and only 1 or 2 lung metastases, which have been stabilised for 6 months after per-operative evaluation.

The absolute contraindications to surgical resection are determined both by the technical inability to resect all metastases and by the presence of extrahepatic metastases that cannot be radically resected; therefore when it is not possible to perform an R0 radical resection.

The presence of metastatic lymph nodes at the hepatic hilum is associated with a poor prognosis even after a complete lymph node resection [46]. In selected patients complete hepatoduodenal ligament and hepatic artery lymph node resection with adjuvant chemotherapy might have good results. However, some Authors failed to observe any prognostic advantage of this strategy [32].

Distant extrahepatic metastases are usually considered as an absolute contraindication to surgery, but there are advantages of en-bloc resection of hepatic and extra-hepatic metastases for patients with tumour invasion of adjacent structures.

Many guidelines are reported in the literature and those published by the National Comprehensive Cancer Network [47] are frequently utilised in clinical practice. These guidelines have defined criteria for surgery resectability and actual models for multimodality treatment including adjuvant or neoadjuvant chemotherapy (Tables 4, 5).

Results

Nowadays surgical resection represents the only therapeutical option that may achieve a radical treat-

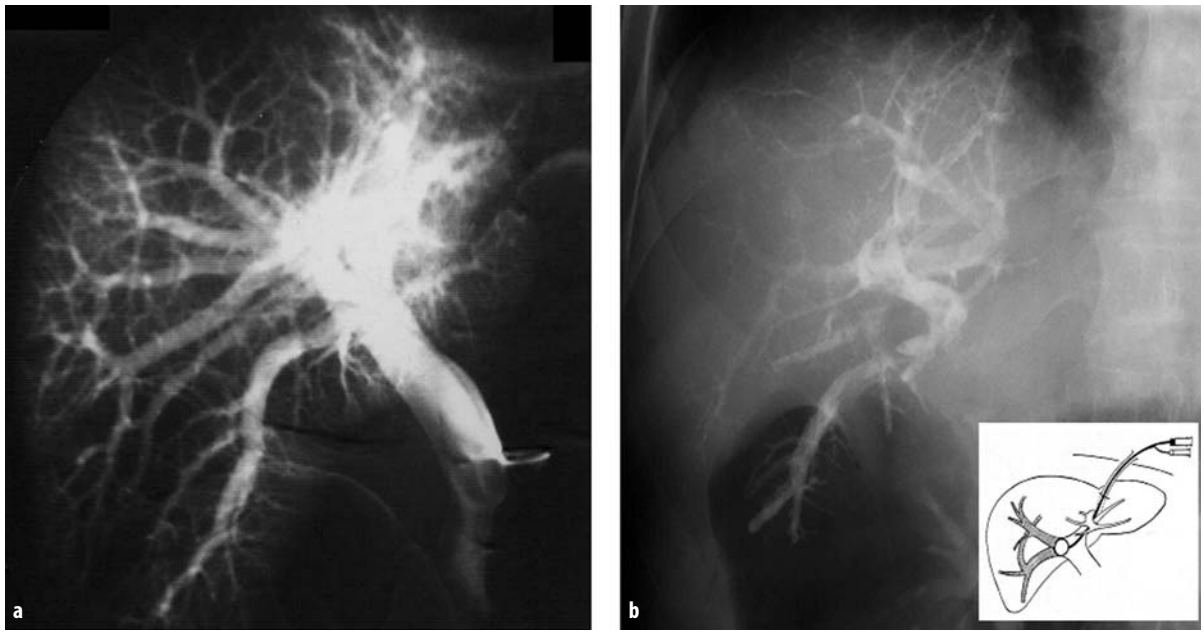

Fig. 2a, b. Portal vein embolisation. **a** Transhepatic portography. **b** Right portal system after injection of fibrin glue. The drawing shows the balloon catheter used for the injection of fibrin glue

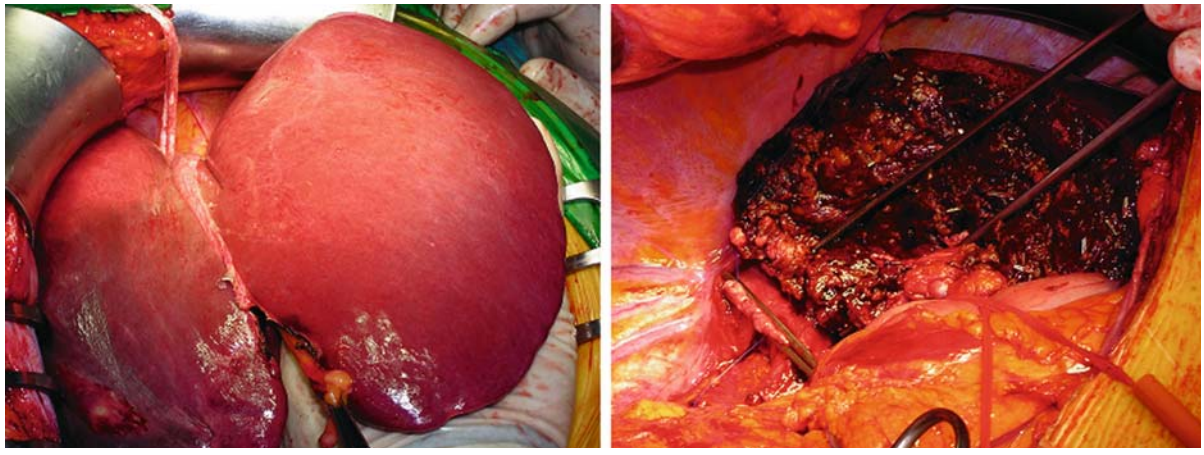

Fig. 3. Left lobe hypertrophy after portal vein embolisation of right portal system. On the right, surgical field after right extended hepatectomy

ment of liver metastases. This procedure allows survival rates that are considerably higher compared with other therapeutical procedures. Surgical resection is effective and effects 5-year survival rates of 26–45% [22], whereas in patients not submitted to surgical resection, 5-year survival is almost zero [48]. Hepatic resection is performed with low morbidity and mortality rates: 0–3% in specialised centres [53].

The most frequent causes of mortality are intra- and post-operative haemorrhage, which occurs in 1–3% of patients. Risk of post-operative hepatic failure is low: 1–5% after major hepatic resections. The more frequently observed *surgical complications* are: pulmonary in 10–20% of patients, biliary tract lesions in 3–5%, infectious in 2–9% and cardiac complications in 1–5% (Table 6). The mean hospital stay in patients submitted to major hepatic resection usually does not exceed two weeks.

Strategies to Increase Metastases Resectability

Only 20% of patients with liver metastases are eligible for hepatic resection. Recently, new strategies to

Table 7. Portal vein embolisation in liver metastases

Study	*n*	PVE to surgery day	FRLV			% Resected
			Before	After	Increase	
De Baere et al. [54]	22	32	19	32	13	77
Azoulay et al., [51]	30	63	26	37	11	63
Kokudo et al. [50]	18	24	38	46	8	100
Elias et al. [58]	68	30	n.a.	n.a.	13	88

PVE, portal vein embolisation; *FVRL*, functional residual liver volume
This series includes 27 patients with liver metastases from other primary tumours

increase the number of patients eligible for curative resection have been proposed: per-operative portal embolisation (PVE) and two-stage hepatectomy [49].

Portal Vein Embolisation (PVE)

In patients with normal liver function, safe hepatic resection should preserve at least 25% of total hepatic volume; in patients submitted to per-operative chemotherapy with chronic liver disease at least 40% of total liver volume should be preserved due to a higher risk of post-operative liver failure [50, 51]. When planned resection exceeds these values, per-operative PVE may be utilised to reduce the risk of post-operative liver failure. PVE was described for the first time in 1990 by Makuuchi et al. [52].

The scope of PVE is to induce compensatory hypertrophy of remnant liver and atrophy of the lobe with tumour induced by closure of one of more of the portal branches in the part of the liver to be resected [53]. The procedure is performed with percutaneous approach under fluoroscopic control. After percutaneous portography, the portal vein branches are embolised by the use of various types of substances associated to contrast agents (Lipiodol® or Urografin®): cyano-acrylate, Gelfoan®, Tissucol®. Among these embolising materials some Authors prefer cyanoacrylate because other substances (Tissucol, Gelfoam) may be reabsorbed a few weeks after the procedure, leading to re-establishment of blood flow [54] (Fig. 2).

Induced compensatory hypertrophy, is assessed after 5 or 6 weeks by CT (Fig. 3).

Portal embolisation induces modifications in hepatic haemodynamics with a considerable increase of portal pressure; similar disturbances are observed after a major hepatic resection. In the embolised part of the liver, absence of portal flow leads to cellular apoptosis, which leads to atrophy of the embolised lobe and to hyperplasia and hypertrophy of the contralateral lobe, determined by active cell proliferation, which increases 2 weeks after PVE. Hepatic hypertrophy is mediated by intra- and extra-hepatic growth factors; the extra-hepatic ones are transported through the portal vein system (insulin, noradrenalin, portal hormones). This response seems to be mediated by the same factors that are responsible for hepatic regeneration after hepatectomy (hepatocyte growth factor, TGF-α, TNF-α and IL-6). The time for maximal hypertrophy after PVE is not clear yet, but it is clear that patients with diabetes or with chronic liver disease need a longer period to obtain hypertrophy, at least 6–8 weeks [55, 56].

PVE is usually well tolerated and determines only a low inflammation of the periportal space. Patients usually suffer mild side effects: fever, nausea, slight abdominal pain and mild temporary alteration of total bilirubin levels [52]. Abdalla et al. [57] reported side effects in less than 15% of patients, including haemobilia, sepsis and the need to repeat PVE, whereas mortality following the procedure was almost zero.

In the literature, the time elapsed between PVE and hepatic resection is variable and ranges from 3 to 9 weeks [57].

PVE has proved to be a safe method to increase resectability and reduces the risk of major liver resection (Table 7) [58]. Some Authors suggest that this procedure may favour oncogenesis. Jaeck et al. [59] suggest that hepatic hypertrophy processes after PVE would increase growth of metastases located in the residual hepatic lobe. It was observed that, after PVE, 4–37% of patients are ineligible for liver resection due to neoplastic progression. In order to decrease the risk of progression of the tumour after PVE, it would be useful to treat patients with chemotherapy until surgery [60].

Two-Stage Hepatectomy

Two-stage hepatectomy is a method to increase resectability in multiple liver metastases involving both hepatic lobes and was described for the first time by Adam et al. [61]. This procedure consists in a surgical strategy that includes two different phas-

Table 8. Site of tumour recurrence after resection

Recurrence site	Frequency (%)
Liver (total)	48
Only liver	41
Liver/peritoneum	2
Liver/lung	5
Lung (total)	26
Only lung	4
Bone	4
Brain	2
Other sites	26

es. In the first phase the highest number of metastases are removed, preferably removing metastases completely in one lobe, but not all of them. In the second phase, after hypertrophy of the remnant liver, the second liver resection with curative intent is performed.

Usually patients are submitted to chemotherapy to control tumour growth after the first liver resection. Some Authors suggest beginning this treatment after at least 3 weeks in order to avoid interference with initial liver regeneration [61].

Two-stage hepatectomy should not be considered when radical resection is not possible even with the second liver resection. The aim of this procedure is to reduce the risk of post-operative liver failure, as the second liver resection is performed only after adequate hypertrophy of remnant liver.

Two-stage hepatectomy may be associated with PVE or with intraoperative ligation of portal vein of one lobe.

The most appropriate timing for the second hepatic resection takes into account the functioning of liver regeneration and the extent of the planned resection: 1–2 months are usually necessary to achieve 80% hepatic regeneration.

Results of this procedure are good, with a 3-year survival of 35% for patients submitted to radical second liver resection, whereas post-operative mortality is still high and reaches 15% after the second hepatectomy [61].

Surgical Strategy for Recurrence of Liver Metastases

Recurrence of liver metastases is usually observed within two years of liver surgery [62, 63]. The most frequent sites of recurrence after liver resection are reported in Table 8.

After accurate staging of liver recurrence in relation to tumour stage, patients may be submitted to liver re-resection, ablative technique or chemotherapy.

Re-resection is feasible in only 20% of patients. Results of re-resection are comparable with those of the first hepatectomy in terms of mortality and morbidity. Long-term results are good, with 5-year survival ranging from 16 to 57%. Further recurrences may be submitted to repeated liver resection with good results when radical resection is feasible [22, 64].

Local ablative techniques, mainly radiofrequency ablation, have been applied in this particular setting. Local efficacy of these therapies are good for small lesions but efficacy in terms of survival is not clear, even though some authors reported results comparable with surgical resection [67].

Only surgery, nowadays, guarantees good long-term survival in the case of tumour recurrence.

Interstitial Ablative Therapies

Cryoablation

Cryoablation is one of the local ablation techniques that have been used for several years. Low temperatures (from –20 to –30°C) cause direct freezing of tissue, denaturation of cell proteins, rupture of cell membranes, cell dehydration and ischaemic hypoxia that lead to the destruction of the neoplastic tissue. Cryoablation can be performed during laparotomy, or less frequently, during a laparoscopy. Ultrasound is utilised for real-time monitoring of the procedure. The technique consists in the insertion of a probe with a 5–10-mm diameter into the tumour; a cryogenic liquid (usually composed of liquid nitrogen at a temperature of –196°C) is then injected into the probe. Ultrasound is useful to monitor the extension of the frozen area. Usually 1 cm of healthy tissue is included in the frozen area in order to obtain complete treatment of tumour. For larger tumours multiple probes are utilised. Usually treatment consists in 1 or 2 cycles of freezing lasting 5–15 min, then the cryogenic probe is heated and pulled out of the site. The insertion site of the probe is compressed to achieve haemostasis.

Maximal extension of necrosis utilising 10-mm probes is about 7 cm. The size and shape of the necrotic area may be altered by anatomic factors such as the presence of vessels that due to the effect of the blood flow do not allow freezing. The efficacy of the treatment is assessed with imaging techniques (CT or MRI) and with a periodical dosage of tumour markers. Nowadays indications for cryotherapy are limited because this technique has been replaced by other ablation techniques.

The limitations of cryoablation are related to the need for a laparotomic or laparoscopic approach and the occurrence of major complications in about 10% of cases. Major complications after treatment are: post-operative bleeding due to vessel rupture after

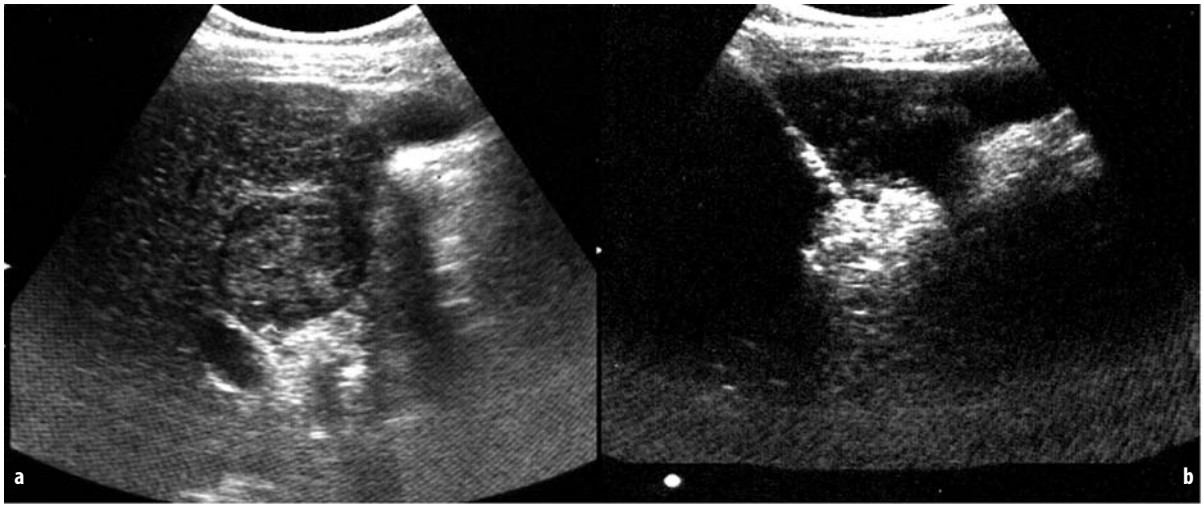

Fig. 4a, b. RFA of liver metastases. **a** Before treatment the lesion is hypo-isoechoic. **b** After treatment the lesion becomes hyperechoic

freezing, right pleural effusion, infection of necrotic area, biliary lesions with fistula and biliomas, thrombocytopenia, myoglobinuria with acute renal failure and DIC (cryoshock phenomenon). Mortality after the procedure is about 1–4%. Data on long-term response report local recurrences in 15% of patients and a 5-year survival for patients with hepatic metastases from colorectal cancer of 10–20%.

Percutaneous Ethanol Injection (PEI)

Ethanol injection is the most widely used interstitial technique to treat primary liver tumours. The use of PEI to treat secondary liver tumours has shown poor effectiveness.

The intralesional injection of alcohol causes cell dehydration and tissue ischaemia due to thrombosis of the neoplastic vessels caused by the necrosis of the endothelial cells and by platelet aggregation. The poor effectiveness of PEI in the treatment of metastasis is probably due to the higher presence of the fibrous tissue, limiting the diffusion of alcohol.

PEI is used in small lesions (<5 cm) and complete response can be achieved in about 50% of lesions of colorectal metastases after multiple treatments. For this reason, use of this treatment for colorectal metastasis is very limited and controversial; more recently PEI was replaced by thermo-ablation.

Thermo-Ablation

Techniques using heat to destroy the neoplastic tissue are multiple. Cell death occurs during exposure to temperatures over 50°C. High temperatures cause protein denaturation and destruction of cell membranes. The techniques used to create thermic injuries are based on the use of radiofrequencies, microwaves and laser.

Thermo-Ablation with Radiofrequency (RFA)

RFA is based on thermic destruction of the tumour induced by the application of alternating current at radiofrequency frequency (350–500 kHz). The passage of the current causes ionic agitation of the tissue, which is converted into frictional heat. Electricity is supplied via an electrode needle inserted into the tumour. At present, many models of electrode-needle are used: single or multiple electrode internally cooled needles (Tyco Healthcare, Mansfield, MA, USA) or retractable multiple electrode non-cooled prongs (Radiotherapeutics and RITA Medical Systems, Mountain View, CA, USA). Experimental studies of comparison among the various models of equipment did not show significant differences in the extent of necrosis [65].

With the equipment used nowadays, the extent of necrosis after a single treatment is about 3–4 cm. For larger lesions multiple insertions of the needle are required. RFA treatment may be performed through percutaneous, laparoscopic and laparotomic approaches. Ultrasound is utilised for real-time monitoring of correct position of the probe into the tumour but also CT or MRI may be used (Fig. 4).

In colorectal metastases, indications for RFA are limited, because only surgical resection allows a radical treatment. RFA effectiveness has not been con-

Table 9. Results of RFA Treatment

Authors	No. patients	Mean size	Mean follow-up (months)	Local recurrences (%)	Intrahepatic or extrahepatic recurrences (%)	1-2-3- years survival (%)
Curley et al. [70]	75	3.4	15	3	30	–
Wood et al. [71]	70	2	9	7	18	–
De Baere et al. [72]	68	2.5	14	10	50	94 ;– ;–
Solbiati et al. [73]	69	4	36	10	58	90; 60; 34
Bowles et al. [69]	117	2.5	18	39	66	93; 69; 46
Pawlik et al. [74]	112	<2	21	2.3	57	98; 70; 50
Mutsaerts et al. [75]	48	2.5	11	7	56	–

firmed in randomised clinical trials and the use of this methodology should be reserved for selected patients. The indications of a mini-invasive treatment in the literature are not standardised and only patients with lesions that are not candidates for surgery are submitted to RFA. Therefore the use of this methodology in otherwise resectable patients should be limited as much as possible.

At the moment the role of RFA is not clear in patients with a non-resectable disease who are treated with combination therapy with RFA and new chemotherapeutic drugs. The use of RFA in association with surgical resection may allow a consensual treatment of multiple lesions in order to achieve the complete treatment of all lesions [66, 67].

The use of RFA in the treatment of recurrences after surgical resection is still controversial, because, despite reiterated surgical resection having the best results, RFA might represent an alternative technique in selected patients. In non-randomised studies, RFA allowed results in these patients in terms of survival comparable with reiterated hepatic resections [63].

Results

RFA, in a review of 3670 patients, proved to be safe and have low mortality rates (0.5%) and a low number of major complications (8.9%); the complications most frequently found were: abdominal bleeding (1.6%), injuries of the biliary tract (1%), injuries of other viscera (0.5%), vascular injuries (0.6%), lung complications (0.8%) and tumoral seedings along the needle insertion site (0.2%) [68].

Data about RFA treatment of hepatic metastases are limited and the results are affected by short follow-up. The response evaluation and local recurrence rate are heterogeneous and do not allow accurate comparisons. The Table 9 lists the most important series of treatment of colorectal metastases. From these results we point out that that tumour size is an important factor for local effectiveness of the treatment. For lesions smaller than 3 cm, the rate of complete response is higher than 90% with local recurrences in less than 10%. For larger lesions, efficacy is lower and local recurrences reach 30% [69]. Despite the good results in terms of local effectiveness, for metastases smaller than 3 cm there are no data about effects on improving survival.

Microwaves

The principles of microwave ablation are similar to those described for RFA. Microwaves cause a high frequency rotation (about 2500 MHz) in the water molecules contained in the tissue, causing it to overheat. Microwaves are emitted through the end of an electrode inserted into the tumour under ultrasound monitoring. This procedure may be performed with a percutaneous or laparotomic approach. A single application lasts about 60 s and produces an elliptical necrosis of about 2 cm around the end of the electrode. For the ablation of masses of larger size, multiple applications are necessary. Indications for microwave ablation are similar to the ones of other thermo-ablation techniques, but its effectiveness is limited to lesions larger than 2 cm. The results in treatment of metastases are still under evaluation, although they seem similar to other thermo-ablation techniques. The complete necrosis of lesions is achieved in about 50–60% of patients and the complication rates are similar to those for RFA.

Laser

The basic principles of laser treatment are similar to other ablative techniques. The laser type most fre-

quently utilised is Nd:YAG. The energy is emitted by optical fibres, which are positioned in the tumour under ultrasound monitoring. Each fibre, with a power of 2–2.5 W, produces a sphere-shaped coagulative necrosis with a 1.5–2 cm diameter. To increase the size of the treated area, several methods have been used, such as the instantaneous application of more fibres or the cooling of the fibre end. The indications for treatment with laser therapy are similar to those for other thermo-ablation techniques. The treatment may be applied with a percutaneous approach with ultrasound, CT or RM. Post-operative mortality is zero and complications observed in the post-operative phase are rare and usually slight (pain, pleural effusions, hepatic abscesses). Moreover, occasional cases of neoplastic seedings along the needle tract have been reported in the literature. The results are similar to those achieved with other thermo-ablation methods, with a more limited effectiveness in lesions larger than 3 cm. A peculiarity in the use of the laser is its complete compatibility with MR equipment.

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Chemotherapy for Metastatic Rectal Cancer

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Introduction

Many modalities have been evaluated for the treatment of metastatic colorectal cancer: systemic chemotherapy, regional chemotherapy, ablative therapies, surgery and combined strategies. Systemic chemotherapy is the most widely used approach and for many years has been considered only in a palliative setting. After four decades 5-fluoruracil remains the mainstay of treatment with its different biomodulations and infusional regimens. However the availability of active new drugs such as irinotecan, oxaliplatin and raltitrexed, oral agents such as capecitabine and uracil-tegafur (UFT), and more recently the development of targeted molecular therapies such as cetuximab and bevacizumab has permitted the oncologist to leave behind nihilism and enter a promising new age.

About 50% of patients diagnosed with colorectal carcinoma have metastatic disease at the time of diagnosis or will develop metastases or local recurrences after diagnosis.

Rectal cancer requires a different approach to colon cancer in the pre-operative and adjuvant settings: metastatic diseases have the same treatment and randomised or phase II trials include both tumours.

This chapter reviews the evidence and focuses on state of the art research and everyday treatment of patients with metastatic rectal cancer.

5-Fluorouracil (FU)

Fluorouracil (FU), discovered in 1957 [1], has been considered to be the standard therapy for the palliative treatment of metastatic colorectal cancer for about 40 years. The overall response rate when used as the single agent is about 20% and complete responses are extremely rare with a median survival less than 12 months. One review of trials of new agents in colorectal cancer between 1960 and 1990 found that none of the 72 compounds evaluated produced a higher response rate than FU [2]. One way to attempt to increase the mechanisms of action of FU was biomodulation. A number of biomodulation strategies have been used with FU: methotrexate with a higher response rate (19% vs. 10%) and a 1.6-month survival advantage (p=0.024) [3]; interferon-α without any documented advantage [4]; and finally leucovorin calcium (LV), which has been the most widely used agent for biomodulation. When compared with the best supportive care, the combination FU–LV showed a significantly longer survival (11 vs. 5 months) [5].

The best known regimens, Machover (a daily×5 schedule of FU 370 mg/m^2 with LV 200 mg/m^2 every 4 weeks), Roswell Park (a weekly schedule of FU 600 mg/m^2 with LV 500 mg/m^2) and Mayo Clinic (a daily×5 schedule of FU 425 mg/m^2 with LV 20 mg/m^2 every 4 weeks), showed 20–30% increased response rates with different kinds of toxicity: mucositis in the first and diarrhoea in the second [6, 7].

At least a dozen randomised trials have addressed the question of whether FU plus LV is superior to FU alone. The updated meta-analysis has show the advantage of FU-LV over FU alone is not limited to tumour response (21% for the combination and 11% for FU alone) but also applies to overall survival, with a median survival time of 10.5 months for patients treated with FU alone and 11.7 months for patients treated with FU–LV (p=0.004) [8].

A North Central Cancer Treatment Group study compared two leucovorin schedules: Mayo Clinic low-dose, daily×5 and the Roswell Park weekly high dose. There were no significant differences in therapeutic efficacy between the two regimens tested with respect to the following parameters: objective tumour response (35% vs. 31%), survival (median 9.3 vs. 10.7 months) and palliative effects (as assessed by relief of symptoms, improved performance status and weight gain). There were significant (p<0.05) differences in toxicity, with more leukopenia and stomatitis seen with the intensive-course regimen, and more diarrhoea and requirement for hospitalisation to manage toxicity with the weekly regimen. Finan-

Table 1. FU evolution in the treatment of metastatic colorectal cancer

Author	Trial	Response rate (%)	Median survival (months)	1-year survival (%)
Scheitauer et al. [5]	FU+LV		11 pS	–
	BSC		5	–
Meta-analysis [3]	FU+LV	21 pS	11.7	47 pS
	FU	11	10.5	37
Buroker et al. [9]	FU+HDLV	35	9.3	–
	FU+LDLV	31	10.7	–
Meta-analysis [10]	FU CI	22 pS	12.1 pS	–
	FU	14	11.3	–
De Gramont et al. [11]	FU+LV2	32 pS	15.5	–
	FU+LV	14.5	14.2	–

pS, *p* value statistically significant

cial cost was also higher with the weekly regimen [9].

FU has been shown to have a short plasma half-life of 8–20 min following a bolus injection and these observations led to the development of different infusional schedules classically divided in two categories: protracted intravenous (IV) and high-dose intermittent infusions. These have been compared with bolus schedules in randomised trials.

FU continuous infusion (CI) is superior to FU bolus in terms of tumour response and achieves a slight increase of overall survival. The haematologic toxicity is much less important in patients who receive FU CI, but hand-foot syndrome is frequent in this group of patients [10].

The intermittent high dose was more effective and less toxic than the monthly regimen and definitely increased the therapeutic ratio. However, there was no evidence of increased survival [11] (Table 1).

New Drugs

In the late 1990s the incorporation of irinotecan (CPT-11) and oxaliplatin in the management of advanced colorectal cancer generated further improvement in survival. Combinations of FU and LV with irinotecan (FOLFIRI, IFL) or oxaliplatin (FOLFOX4, FOLFOX6) are considered to be standard first-line chemotherapy treatment.

Irinotecan

Irinotecan (CPT-11) is a campthotecin derivative with anti-tumour activity via inhibition of topoisomerase-I, a nuclear enzyme that facilitates DNA uncoiling for replication and transcription by binding to DNA and causing reversible single-stranded DNA breaks. Because of the different mechanism of action from that of FU, at the beginning it was evaluated in FU-refractory disease.

A total of 304 patients with FU-refractory colorectal tumour had a major response rate of 13% with 49% of minor response or stable disease when treated with weekly doses of 125 mg/m^2 for 4 weeks followed by a 2-week break. Diarrhoea and neutropenia were the major dose-limiting toxicities [12].

In two European trials CPT-11 has been compared to best supportive care or retreatment with FU CI in patients with colorectal cancer refractory to FU bolus. The CPT-11 schedule of 350 mg/m^2 every 3 weeks was used for these trials.

In the first study the overall survival was significantly better in the CPT-11 group (1-year survival of 36.2% and 13.8% respectively in CPT-11 and supportive care arms, p=0.0001). In a quality of life (QoL) analysis, all significant differences, except on the diarrhoea score, were in favour of the CPT-11 group [13].

In the second study, patients treated with CPT-11 lived for significantly longer than patients treated with FU (p=0.035). Survival at 1 year was increased from 32 to 45% and median survival from 8.5 to 10.8 months in the CPT-11 group. Median progression-free survival was longer with CPT-11 (4.2 *vs.* 2.9 months, p=0.030). Both treatments were equally well tolerated and QoL was similar in both groups [14].

Another phase III trial has investigated the efficacy and tolerability of two CPT-11 dosing regimens (weekly 125 mg/m^2 for 4 weeks or once 300–350 mg/m^2 every 3 weeks) in patients with FU-refractory colorectal cancer. There was no significant difference in 1-year survival (46% *vs.* 41%, respectively, p=0.42), median survival (9.9 *vs.* 9.9 months, p=0.43) or median time to progression (4.0 *vs.* 3.0 months, p=0.54) between the two regimens. Every 3-week regimen was associated with a significantly lower incidence of severe diarrhoea (p=0.002). Treatment-related mor-

Table 2. Phase III randomised trials of CPT-11 in patients with metastatic colorectal cancer

Authors	Trial	Response rate (%)	Progression-free survival (months)	Median survival (months)
Cunningham et al. [13]	CPT+BSC	–	–	9.2
	vs. BSC	–	–	6.5
Rougier et al. [14]	CPT-11	–	–	10.8
	FU CI	–	–	8.5
Saltz et al. [16]	CPT-11+FU+LV	39 pS	7.9 pS	14.8 pS
	FU+LV	21	4.3	12.6
	CPT-11	18	4	12
Douillard et al. [17]	CPT-11+FU+LV	49 pS	6.7 pS	17.4 pS
	FU+LV	31	4.4	14

pS, *p* value statistically significant

tality occurred in 5.3% receiving weekly CPT-11 and in 1.6% receiving CPT-11 every 3 weeks [15].

CPT-11 was then introduced in the first line for the treatment of previously untreated colorectal cancer. Three phase III prospective randomised trials were designed to compare the efficacy and toxicity of the combination of FU, LV and CPT-11 to FU and LV alone.

The American trial compared bolus FU–LV–CPT-11 (IFL) to bolus FU-LV and to CPT-11 alone. The trial demonstrated significant benefit in terms of confirmed response rates, progression-free survival and overall survival. IFL showed confirmed responses in 39% of patients, compared with 21% in patients treated with FU–LV and 18% in patients treated with CPT-11 ($p<0.001$). In addition, progression-free survival was significantly prolonged with IFL (7.9 vs. 4.3 months, $p=0.004$). Median survival was also improved: 14.8 months for IFL and 12.6 months for FU–LV ($p=0.042$) [16].

The first European trial compared CPT-11, using AIO or Douillard regimen (weekly or every 2 weeks infusion) with infusional FU–LV using the same schedule. The CPT-11 regimen had a significantly longer time-to-progression (median 6.7 months vs. 4.4 months, $p<0.001$), a higher response rate (49% vs. 31%, $p<0.001$) and a higher overall survival (median 17.4 vs. 14.1 months, $p=0.031$) [17] (Table 2).

Oxaliplatin

Oxaliplatin is a novel diaminocyclohexane platinum analogue that acts mainly by causing interstrand and intrastrand cross-links in DNA. Alone or combined with FU and LV, it has shown promising activity in previously treated and untreated patients with metastatic colorectal cancer and in patients with FU refractory disease.

Three phase III prospective randomised trials compared the efficacy of the combination OXA–FU–LV to FU–LV.

The first study compared FOLFOX regimen (oxaliplatin 85 mg/m^2 as a 2-hour infusion on day 1 and 2-hour infusion of LV 200 mg/m^2/day followed by a FU bolus 400 mg/m^2/day and 22-hour infusion 600 mg/m^2/day for 2 consecutive days every 2 weeks) to the same regimen of infusional FU-LV alone in previously untreated patients with advanced colorectal cancer. Patients treated with FOLFOX4 had a significantly longer progression-free survival (9.0 vs. 6.2 months, $p=0.0003$) and response rate (50.7% vs. 22.3%, $p=0.0001$), but no improvement in overall survival (16.2 vs. 14.7 months, $p=0.12$). Grade 3 and 4 toxicity (neutropenia, diarrhoea and neuropathy) were more common in the oxaliplatin arm but this did not result in impairment of QoL. Survival without disease progression or deterioration in global health status was longer in patients allocated to oxaliplatin treatment ($p=0.004$) [18].

Similar results were observed in a second randomised trial using a chronomodulated schedule. Sixteen percent of the patients receiving FU-LV had an objective response, compared with 53% of those receiving additional oxaliplatin ($p<0.001$). The median progression-free survival time was 6.1 months with FU–LV and 8.7 months with oxalipaltin and FU–LV ($p=0.048$). Median survival times were 19.9 and 19.4 months, respectively [19].

A third phase III study randomised between FU bolus 425 mg/m^2, LV 20 mg/m^2, on days 1–5, repeated every 4 weeks; and oxaliplatin 50 mg/m^2, 2-h infusion, FU 2000 mg/m^2, 24-h infusion, LV 500 mg/m^2 on days 1, 8, 15, 22, repeated every 5 weeks (FUFOX regimen). Response rate was more than doubled in FUFOX with 48.3% vs. 22.6% ($p<0.0001$) and 8.8% of complete response in FUFOX. After a median follow-up of 27.3 months, progression-free survival is signif-

Table 3. Phase III randomised trials of oxaliplatin in patients with metastatic colorectal cancer

Author	Trial	Response rate (%)	Progression-free survival (months)	Median survival (months)
De Gramont et al. [18]	FOLFOX	50.7 pS	9 pS	16.2
	FU–LV	22.3	6.2	14.7
Giacchetti et al. [19]	FU–LV+OXA chrono	53 pS	8.7 pS	19.9
	FU–LV	16	6.1	19.4
Grothey et al. [20]	FUFOX	48.3 pS	7.9 pS	20.4
	FU–LV	22.6	5.3	16.1

pS, *p* value statistically significant

icantly longer in the oxaliplatin arm: 7.9 *vs.* 5.3 months ($p<0.0001$). Median overall survival is 20.4 and 16.1 months respectively [20] (Table 3).

Two North American randomised phase III trials have evaluated a second chemotherapeutic line with a regimen containing oxaliplatin in patients with progressive metastatic colorectal cancer after front-line treatment with CPT-11, bolus FU–LV. In the first FOLFOX was found to be superior in response rate (9.6%) to oxaliplatin (1.1%) and FU–LV (0.7%) alone. Mature data from this study, however, failed to show a statistically significant improvement in median survival. Toxic effects, particularly neutropenia and neuropathy, were higher in the FOLFOX arm but these toxicities were predictable and did not result in a higher rate of treatment discontinuation or 60-day mortality rate [21].

In the second, FU–LV with or without oxaliplatin was evaluated in patients with metastatic colorectal cancer after disease progression on sequential fluoropyrimidine and CPT-11. FOLFOX was found to be superior to FU–LV in terms of: response rates (13% vs. 2%, $p=0.0027$), median time to disease progression (4.8 vs. 2.4 months, $p<0.0001$) and median survival (11.4 vs. 9.9 months, $p=0.20$). Symptomatic improvement was significantly better for FOLFOX (32% vs. 18%, $p=0.05$) [22].

The next generation of studies compared CPT-11-based to oxaliplatin-based chemotherapy in patients with newly diagnosed advanced colorectal cancer.

GERCOR group compared FOLFOX with FOLFIRI in patients with advanced colorectal cancer. In this study, patients were crossed over from 1 regimen to the other at the time of progression. These 2 first-line treatments for metastatic and advanced colorectal cancer have demonstrated similar response rates and acceptable toxic effects profiles with no differences in median time-to-first progression (8 vs. 8.5 months) or overall survival (20.6 *vs.* 21.5 months) for FOLFOX followed by FOLFIRI regimen *vs.* FOLFIRI followed by FOLFOX regimen. A response rate of 15% and a median progression-free survival of 4.5 months were seen in patients who progress to FOLFIRI chemotherapy when treated with FOLFOX, and a response rate of 4% with a median progression-free survival of 2.5 months for the reverse sequence [23].

The US Cooperative Groups completed a randomised intergroup clinical trial for the first treatment of advanced colorectal cancer. This trial was originally launched to compare IFL, FOLFOX and a combination of oxaliplatin and CPT-11 with Mayo regimen. A total of 795 patients were randomised. With a median follow-up of 20.4 months, all outcome measures for FOLFOX were significantly better than IFL, including a significantly better time-to-tumour progression (8.7 vs. 6.9 months, $p=0.0014$), a higher response rate (45% vs. 31%, $p=0.002$) and an improved overall survival (19.5 vs. 15 months, $p=0.0001$). Patients treated with irinotecan and oxaliplatin (IROX) had a significantly lower median time-to-progression (6.5 months) and response rate (35%) compared to FOLFOX ($p=0.001$ and $p=0.03$, respectively); median survival, however, did not differ significantly between the 2 regimens (19.5 vs. 17.4 months, $p=0.09$).

The results of this study establish the FOLFOX regimen as the first-line treatment in advanced colorectal cancer [24].

The last generation of trials evaluated the triplet combination of CPT–oxaliplatin–FU in patients with newly diagnosed or pretreated metastatic colorectal cancer. A biweekly regimen with oxaliplatin, CPT-11, infusional FU and LV (FOLFOXIRI) showed a response rate of 71.4% and 26% of patients were downstaged and surgical resection could be performed; median progression-free and overall survival times were 10.4 and 26.5 months, respectively. The pharmacokinetics parameters of the agents used and their metabolites did not seem to be influenced by the concomitant use of the other drugs. The most relevant toxicities were diarrhoea and neutropenia [25] (Table 4).

Table 4. Comparative, sequential and integrated trials of CPT and OXA

Author	Trial	Response rate (%)	Progression-free survival (months)	Median survival (months)
Tournigand et al. [23]	FOLFOX–FOLFIRI	56	8.1	20.4
	FOLFIRI–FOLFOX	57.5	8.5	21.5
Goldberg et al. [24]	IFL	31	6.9	15
	FOLFOX	45 pS	8.7 pS	19.5
	IROX	34	6.5	17.4
Falcone et al. [25]	FOLFOXIRI	71.4	10.4	26.5

pS, *p* value statistically significant

Tomudex

Raltitrexed is a specific thymidylate synthase inhibitor which has demonstrated activity similar to that of bolus FU and LV for the first-line treatment of advanced colorectal cancer. The recommended dose is 3.0 mg/m^2 every three weeks. Median survival and response rate were comparable to that of bolus or infusional FU–LV. As with other cytotoxic agents, serious and potentially life-threatening side effects can occur: particularly diarrhoea and neutropenia. The incidence of serious side effects may be minimised with the assessment of renal function before and after every treatment and dosage adjustment in the presence of renal impairment [26].

Oral Chemotherapy

A protracted continuous infusion of FU has the advantages of a different and milder toxicity, but there is the drawback of the need of a central venous system for infusion and the discomfort of carrying an infusion pump. Oral regimens using prodrugs of FU pharmacologically simulate continuous infusion and are under clinical evaluation. Furthermore, patients receiving therapy for late-stage disease prefer oral rather than IV chemotherapy (IVC) but are unwilling to accept a lower response rate or a shorter duration of response to their preferred choice of oral chemotherapy.

Capecitabine

Capecitabine is an oral fluoropyrimidine carbamate that is converted by thymidine phosphorylase (TP) into FU: because TP levels may be higher in tumour than in normal tissue, a specific therapeutic advantage was possible [27]. A substantial efficacy with an acceptable toxicity profile was documented in a phase II study [28].

A total of 1207 patients with previously untreated metastatic colorectal cancer were randomised to either oral capecitabine (1250 mg/m^2 twice daily, days 1–14 every 21 days) or IV bolus FU–LV (Mayo regimen). Capecitabine demonstrated a statistically significant superior response rate compared with FU–LV (26 vs. 17%, $p<0.0002$). The median time to response, duration of response, time to progression and overall survival were equivalent in the two arms (median 12.9 *vs.* 12.8 months); an improved safety profile was observed and improved convenience compared with IV FU–LV as first-line treatment for metastatic colorectal cancer [29].

Uracil–Tegafur (UFT)

Another oral agent is a combination of uracil and the fluoruracil prodrug tegafur. Uracil is a competitive inhibitor of dihydropyrimidine dehydrogenase that is the rate-limiting enzyme in the catabolism of FU. UFT has been studied in combination with oral leucovorin.

A total of 380 patients were randomised to receive either UFT (300 mg/m^2/day) and LV (90 mg/day), administered for 28 days every 35 days, or FU (425 g/m^2/day) and LV (20 mg/m^2/day), given IV for 5 days every 35 days. There were no statistically significant differences in survival, tumour response, duration of response and time to response. Substantial safety benefits were observed in patients treated with UFT-LV [30].

Targeted Therapy

Interference with the activation of growth factor receptors and/or with the intracellular growth factor-activated signal transduction pathways represents a promising strategy for the development of novel and selective anti-cancer therapies.

Two of the most promising new targets in the

treatment of colorectal cancer are the epithelial growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF). Agents that inhibit the EGFR or bind to VEGF have demonstrated clinical activity as single agents and in combination with chemotherapy in phase II and phase III clinical trials.

Cetuximab

Cetuximab is a monoclonal antibody that specifically blocks the EGFR. The efficacy of cetuximab in combination with CPT-11 or alone was evaluated in a randomised trial in metastatic colorectal cancer refractory to treatment with CPT-11. Three hundred and twenty-nine patients whose disease had progressed during or within three months after treatment with a CPT-11-based regimen were randomly assigned to receive either cetuximab and CPT-11 (at the same dose and schedule as in a pre-study regimen) or cetuximab monotherapy. The rate of response in the combination therapy was significantly higher than that in the monotherapy (22.9% vs. 10.8%, p=0.007). The median time to progression was significantly greater in the combination therapy (4.1 vs. 1.5 months, p<0.001). The median survival time was 8.6 months for the combination-therapy and 6.9 months for the monotherapy (p=0.48). Toxic effects were more frequent in the combination therapy group, but their severity and incidence were similar to those that would be expected with CPT-11 alone. Cetuximab has clinically significant activity when given alone or in combination with CPT-11 in patients with CPT-11-refractory colorectal cancer [31].

Bevacizumab

Bevacizumab is a humanised variant of the anti-VEGF monoclonal antibody that has been studied as an anti-angiogenic cancer therapeutic as a single agent and in combination with chemotherapy in patients with stage III and IV colon cancer. In addition to its direct anti-angiogenic effects, bevacizumab may allow more efficient delivery of chemotherapy by altering tumour vasculature and decreasing the elevated interstitial pressure common in tumours. Eight hundred and thirteen patients with previously untreated metastatic colorectal cancer were randomly assigned to receive IFL plus bevacizumab (5 mg/kg body weight every two weeks) or to receive IFL plus placebo. The primary end-point was overall survival. Secondary end-points were progression-free survival, response rate, duration of the response, safety and QoL. Median survival was 20.3 months for IFL plus bevacizumab and 15.6 months for IFL plus placebo (p<0.001). Median progression-free survival was 10.6 months for IFL plus bevacizumab, and 6.2 for IFL plus placebo (p<0.001); response rates were 44.8 and 34.8% (p=0.004) in favour of the patients treated with IFL plus bevacizumab. The addition of bevacizumab to FU-based combination chemotherapy results in statistically significant and clinically meaningful improvement in survival among patients with metastatic colorectal cancer [32].

Liver Metastases

Unlike most other malignancies, colorectal cancer has a potential to metastasise to an isolated distant site, of which the liver is the most common. These locoregional metastases may be treated with surgical or ablative procedures or hepatic arterial chemotherapy (HAC).

Only about 20% of patients presenting with liver metastases are suitable for surgical resection. An adequate response to chemotherapy in advanced colorectal cancer with initially unresectable liver metastases may permit resection of the metastases and the 5-year survival rate is similar to that of initially resectable metastases. In a retrospective analysis of 701 patients with initially unresectable liver metastases, surgery with curative intent was performed in 35% of patients following FU–LV and OXA; the 5-year survival rate was 35% with long-term survival, similar to that in initially curative resection [33]. Liver resection seems associated with a poor outcome if there is tumour progression under chemotherapy and metastatic disease is not controlled prior to surgery [34].

HAC delivers high concentrations of cytotoxic agents directly to liver metastases with minimal systemic toxicities. Randomised trials comparing HAC with systemic chemotherapy have demonstrated superior response rates and times to hepatic progression for unresectable disease. A meta-analysis based on seven trials compared HAC with floxuridine (FUDR) vs. IVC with FUDR or FU *vs.* best supportive care: tumour response rate was 41% and 14% for patients allocated to HAC and IVC respectively (p<0.0001); survival analyses showed a statistically significant advantage for HAI compared with control when all the trials were taken into account (p=0.0009) but not when survival analysis was restricted to trials comparing HAC and IVC (p=0.14) [35].

A recent randomised trial compared HAI with the standard IV de Gramont regimen for patients with metastases confined to the liver. There is no evidence of advantage in overall survival (14.7 and 14.8 months) or progression-free survival (7.7 and 6.7

months). Thus, clinical use of this regimen cannot be recommended and other prospective clinical trials should be conducted to more definitively answer this question [36].

According to the clinical response rate and median survival obtained with the new systemic regimen, phase I and II studies of HAI with oxaliplatin or CPT-11 have already been published. They have demonstrated tolerability and an interesting efficacy in heavily pretreated patients [37, 38].

Elderly Patients

A significant proportion of patients presenting with colorectal cancer are elderly (over the age of 70 years). The Comprehensive Geriatric Assessment, which subdivides the population of elderly cancer patients into three groups, can help to guide treatment decisions. The group of "fit" elderly patients (good performance status or no significant comorbidity) can tolerate a cytotoxic treatment and the use of systemic FU-based chemotherapy has been shown to be of clinical benefit for these patients with metastatic disease in terms of survival, control of symptoms and QoL.

A European analysis of 22 trials with 5-FU-containing treatment found the same survival and response rate in elderly and in younger patients, while progression-free survival was marginally prolonged in the elderly [39]. In a North American analysis of 4 trials testing 5-FU with or without LV, performance status, not age, has been predictive of time to tumour progression and overall survival; elderly patients treated with 5-FU have modestly higher rates of severe toxicity, mainly diarrhoea and stomatitis [40].

Data from the first clinical trials regarding the use of new drugs (oxaliplatin, irinotecan, raltitrexed, oral fluoropyrimidines) in selected elderly patients are limited but indicate an activity comparable to that observed in younger patients, with overall manageable toxicity.

In conclusion, standardised palliative chemotherapy should generally be offered to fit elderly patients and they should not be excluded from clinical trials in order to gain information about new treatments.

The Therapeutic Strategy

Generally, patients with a large tumour and several metastatic sites with an ECOG performance status of 2 or greater have a lower chance of response to chemotherapy. For many of these patients the attendance or supportive care is the recommended treatment choice. On the other hand, patients who are in a good general condition with a small tumour, not previously exposed to chemotherapy, have response rates of approximately 50% when treated with CPT-11 and oxaliplatin. The cases in between the two conditions described are more difficult to manage and the approach must be individualised. If the patient is elderly, his general condition is not very good or he does not seek particular medical attention, it is reasonable to wait a month or two, check the rate of disease progression and withhold treatment until later in the course [41].

More debatable is the issue of treatment of the non-symptomatic patient. As the end-point of treatment is palliation, should we wait until symptoms develop (so that there is something to palliate) or should treatment be instituted right away? Several phase III studies concluded that patients who are treated at diagnosis of metastatic disease with conventional FU-based regimens live significantly longer (by 3–6 months) than patients in whom chemotherapy is delayed until symptoms develop; even if the overall response rate to standard chemotherapeutic regimens is low in unselected patients with advanced colorectal cancer, the subjective benefit is substantial [42].

At this time, there is a role for combination chemotherapy as a first-line treatment in fit patients. Standard systemic chemotherapy for advanced colorectal cancer is the use of combination therapy with oxaliplatin or CPT-11. Only in some cases can FU-LV be considered the best choice. In general there is agreement that bolus FU alone is ineffective and that biochemical modulation is needed for bolus FU activity whereas it is not for protracted infusional FU. Biochemical modulation is also required when using intermittent high-dose infusional FU.

In fit patients chemotherapy is also indicated for second- and in some cases thirdline therapy. Treatment of patients who progress after first-line chemotherapy is guided by which treatment was used for first-line treatment. Patients who were treated with a FOLFOX-based regimen should be treated with a CPT-11-based regimen and patients who already received a CPT-11-based regimen should be treated with a FOLFOX-based regimen.

The GERCOR Group achieved 26-month median overall survival with the sequential use of continuous infusional FU–LV, oxaliplatin and CPT11 combinations in metastatic patients.

The analysis of large phase III trials using FU, CPT11 and oxaliplatin revealed that the higher proportion of patients was treated with all three drugs, the longer overall survival was achieved; the use of combination protocols as first-line chemotherapy was associated with a significant improvement in median survival of 3.5 months (p=0.0083) [43].

The anti-VEGF bevacizumab increases the efficacy of first-line CPT-11 therapy, while the addition of cetuximab restores CPT-11 sensitivity in second-line treatment.

Regarding the duration of chemotherapy for these patients, as long as there are no other factors that contraindicate treatment, chemotherapy should be recommended for approximately 2 months and then their outcome must be evaluated. If the treatment is fairly well tolerated and there is at least a stabilisation of the disease, chemotherapy should be continued until progression or toxicity. Usually in clinical practice chemotherapy is stopped after a maximum of 6 months. A recent trial has compared effectiveness of continuous and intermittent chemotherapy in patients who responded or had stable disease after receiving 12 weeks of the regimens described by de Gramont and Lokich, or raltitrexed chemotherapy: they were randomised to either intermittent (a break in chemotherapy, re-starting on the same drug on progression) or continuous chemotherapy until progression. Patients on intermittent chemotherapy had significantly fewer toxic effects and serious adverse events than those in the continuous group. There was no clear evidence of a difference in overall survival [44]. Another strategy may be the so-called "stop and go therapy". In the OPTIMOX study reintroduction of oxaliplatin was feasible and achieved a response or stabilisation in 73% of patients. These results support the concept that intensified, repeated short courses of FOLFOX are efficacious and less toxic [45].

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