Colorectal cancer — what is standard surgery?

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Introduction

The contribution of standard surgery to the treatment of colorectal cancer means that in patients presenting with a primary tumour after completion of a diagnostic work-up, an algorithm is followed by the interdisciplinary treatment team resulting in allocating the adequate surgical procedure with respect to the tumour stage and the patient's general condition. Within this concept, the decision has to be made, whether surgical treatment alone is adequate or whether surgery needs to be combined with other treatment modalities. The operative procedure needs to be performed with the highest skill available. The surgeon is not just the technical slave of the algorithm, but contributes his/her part of surgical oncology together with the other contributors from medical oncology, radiation oncology, pathology and other cooperating disciplines.

Preoperative diagnostic work-up

Up to 25% of patients with colorectal cancer are admitted for treatment after the development of complications, mostly obstruction or perforation [1–3]. Plain abdominal radiographs reveal the distention of the large bowel proximal to the site of obstruction. If there is doubt as to the diagnosis, a double contrast enema with water a soluble medium is often diagnostic.

The aims of the investigations of a patient suspected of cancer of the colon or rectum are listed in Table 1.

To precisely plan an operative procedure, it is mandatory to know the exact location of the tumour. Colonoscopy is the method of first choice. If it has been performed without X-ray control of the site of biopsy of malignant lesion, an enema is the simplest and most accurate method. To locate the height of a rectal tumour, rigid rectoscopy is the method of choice and it is important to report whether the dentate line or the anal verge was used for reference.

Synchronous primary cancers or adenomas are present in approximately $\frac{1}{3}$ of the patients. Adenomas that are not within the margin of resection should be removed endoscopically and histological findings should preferably be available prior to proceeding with definitive operation. Total colonoscopy with identification of the ileo-caecal valve is required. In case of an obstructing tumour that cannot be passed by colonoscopy, enema with water-soluble contrast media is an alternative. Otherwise, colonoscopy should be performed intraoperatively or within three months postoperatively at the latest.

Preoperative stage classification is of less importance in cancer of the colon, where the indication for tumour resection is always accepted if no widespread distant metastases are present. In rectal cancer, the depth of wall invasion and/or the presence of lymph node metastases need to be evaluated preoperatively as locally advanced tumours should undergo combined modality treatment. Endoluminal ultrasound is the diagnostic tool of choice. Its accuracy is approximately 85–90% regarding the T-category [4–6] according to TNM and approximately 75–85% regarding the nodal status [7]. Endoluminal ultrasound has limited value in assessing the local tumour stage after completion of preoperative radiochemotherapy [8,9]. Approximately 40% of the patients will present overt metastases to the liver, the peritoneum, or the lungs. This may change the therapeutic concept particularly in patients with cancer of the lower third of the rectum.

Table 1
Aims of preoperative diagnostic work-up

- To confirm the site of the primary tumour
- To obtain histological confirmation of the cancer and typing
- To rule out a second primary cancer or colorectal adenomas
- To assess the extent of local and nodal spread, particularly in rectal cancer
- To detect distant metastases

Beyond the mentioned standard tools, computerised tomography to assess extramural spread of colon cancer (depth of invasion) and nodal metastases in rectal cancer is worthwhile if no endoluminal ultrasound is available. In case of obstructing tumours endoluminal ultrasound (EUS) with a miniprobe or the three-dimensional ultrasound are other diagnostic tools to be used where available [10,11]. Endorectal magnetic resonance (MR)-tomography [12,13], 2-[^{18}F]-fluoro-2-deoxy-D-glucose–positron emission tomography (FDG-PET), sentinel node detection, as well as virtual colonoscopy may complete the diagnostic armamentarium in the future. A prospective comparison showed that the accuracy of three-dimensional EUS and endorectal magnetic resonance imaging (MRI) in the assessment of the infiltration depth of rectal cancer is comparable to conventional EUS. One advantage of both methods is the ability to obtain multiplanar images, which may be helpful in planning of surgeries in the future [127].

The tumour marker carcinoembryonic antigen (CEA) (and if negative CA19-9) should be determined preoperatively to be used for postoperative control. There are data reporting an inverse correlation between CEA levels and survival [14], however, this is without preoperative clinical relevance.

Preoperative preparation of the patient includes medical treatment of concomitant diseases and large bowel preparation by mechanical clearance using oral sodium picosulphate lavages. Antibiotic treatment should be single or double shot with a first generation cephalosporin (±metronidazole), delivered during induction of general anaesthesia. Counselling of the patient is of utmost importance, particularly if a colostomy is expected to result from the procedure and the surgeon together with the stoma care nurse should mark the site of the stoma at the abdominal wall to ensure an optimal location.

Decision tree in colorectal cancer

Depending on the preoperative work-up, an indication for the operation must be made. In colon cancer, there is no standard neoadjuvant treatment. Patients with locally advanced tumours with extensions to adjacent organs (T4 lesion) should undergo a multivisceral en bloc resection. Patients with metastatic obstructing colon cancer should undergo resection or a (laparoscopic) bypass procedure to prevent intestinal obstruction at a later stage of disease. At this stage, palliative procedures are often done in patients with poor general condition and perioperative mortality is increased.

In rectal cancer, patients profit from preoperative radio-(chemo-)therapy and endorectal ultrasound as well as intensive clinical staging to assess the local spread, as well as the nodal involvement are decisive elements (Fig. 1).

Specific aspects of surgery in hereditary colorectal cancer

About 15% of patients with colorectal cancer report a family history of this disease. This may occur by chance, or be due to common genetic susceptibility, common exposure to dietary habits or a combination of all these factors. Less than one third of familial cancers have a proven hereditary origin. Germ-line mutations of the *APC* gene located on the long arm of chromosome 5 (5q) are responsible for the autosomal dominant familial adenomatosis polypo-

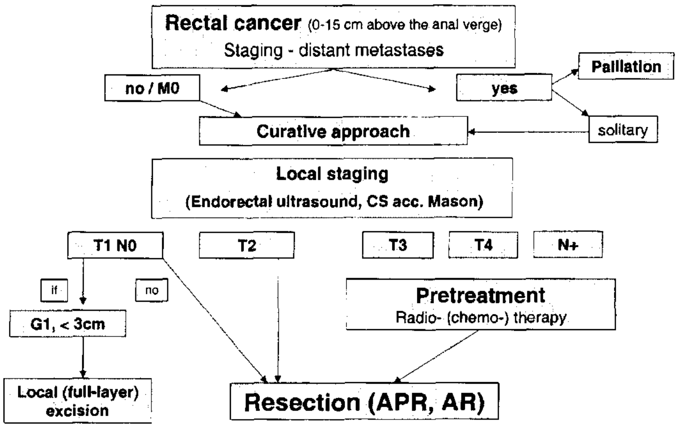

Fig. 1. Algorithm for the operative and neoadjuvant treatment of rectal cancer. CS = clinical staging; APR = abdominal perineal resection; AR = auterior resection.

sis (FAP). The *APC* gene was cloned in 1991 and consists of 15 exons [15]. More than 16 different mutations have been identified so far. The gene product (the APC protein) plays an important role in the regulation of cell-cell interactions by cytoplasmic binding proteins (catenins). Wildtype APC binds free beta-catenin in the cytoplasm and thereby counteracts uncontrolled cell proliferation [16,17]. Sigmoidoscopy reveals numbers of polyps and extracolonic manifestations include adenoma of the upper gastrointestinal tract (GI)-tract, periampullary carcinoma, desmoids, hepatoblastoma, osteoma, and CHRPE (congenital hypertrophy of the retinal pigment epithelium). The indication to restorative proctocolectomy with an ileoanal pouch should preferably be made in patients who are in the second decade of life and can be considered the current standard of care. Vasen et al. [18] evaluated the incidence of rectal cancer in polyposis patients who had undergone ileorectal anastomosis (IRA) and examined whether the requirement for subsequent rectal excision, because of cancer or uncontrollable polyps, was related to the site of mutation of the *APC* gene. The risk of secondary surgery was higher in patients with mutations in the region after codon 1250 of *APC* than in patients with mutations before this codon (relative risk 2.7, $P < 0.05$). If such detailed data are available in an individual patient, it could be considered whether IRA should be the treatment for polyposis in patients with mutations before codon 1250, and restorative proctocolectomy in those with mutations after this codon.

In contrast, hereditary non-polyposis colorectal cancer (HNPCC) might be a syndrome of much more relevance in comparison to FAP. The incidence of the latter is approximately 1/14 000 to 1/16 000 with a penetrance of 100%, accounting for 1% of patients with large bowel cancer. HNPCC might account for 3 to 5% of the so-called sporadic colorectal cancers. The clinical features posed by the dominantly inherited syndromes of HNPCC with a penetrance of 80–90% are less florid and therefore more difficult to recognise than FAP. Two main syndromes have been described and mutations in the DNA mismatch repair genes (most commonly in the *hMSH2* and *hMLH1* genes [19,20]) account for both:

- *Site-specific colon cancer* syndrome with a tendency for tumours to occur at a younger age, to be multiple and more frequently situated in the right colon. But in the individual patient the clinical picture is impossible to differentiate from that produced by sporadic cancers.
- '*Cancer family syndrome*', means that cancer of the large bowel, the endometrium, stomach, upper urinary tract, and ovaries occur within affected families [21,22].

The problem of HNPCC with respect to surgical treatment is that the risk of developing a second colorectal cancer was reported to range from 15 to 30% [23]. Several authors have recommended an extended colonic resection to influence the incidence of second primary tumours. Near total colectomy which leaves the rectum behind and performing an IRA removes the major part of the colonic mucosa at risk for cancer [24–26]. However, complete resection of the primary tumour is always possible also with a less extensive procedure and does not expose the majority of patients to the risk of postoperative morbidity resulting from diarrhoea and malabsorption. There are no prospectively performed studies based on levels of evidence I or II illustrating that the basis of treatment is mainly expert driven. Recommendations by the National Human Genome Research Institute in 1997, as well as from leading experts in the Anglo-American and Scandinavian scientific communities for extended resection are in contrast to more organ-preserving policies, followed often by German-speaking surgeons. Due to the high incidence of interval cancers following negative colonoscopies, the frequency of examinations should be increased [27].

Technical aspects of surgical treatment

Treatment in colorectal cancer shares different aspects: (1) Complete staging followed by radical (R0) surgical resection in patients with curative intent. (2) Prolongation of survival by adjuvant therapy to prevent recurrence or decrease its incidence. (3) Palliation of unresectable primary tumours to improve the patient's quality of life.

In 1975, Turnbull described the 'no touch isolation technique' which avoids tumour cell dissemination intraoperatively during colon cancer resection [28]. He pursued an approach described by Cole in 1954 and compared his results with those surgeons, at the Cleveland Clinic, who continued to use the conventional technique of dividing the vessels after mobilising the tumour. The steps of 'no-touch isolation' were to divide the supplying artery at its origin from the central aorta and to ligate the draining vein to avoid escape of tumour cells during intra-operative manipulation. Occlusion of the colonic lumen was used to eliminate intraluminal spillage and to prevent anastomotic recurrence. Wrapping the tumour with a cytocidal swab was intended to avoid scraping-off tumour cells at the serosal surface. Dissecting the central lymph nodes and not just those of the mesocolon or paracolic

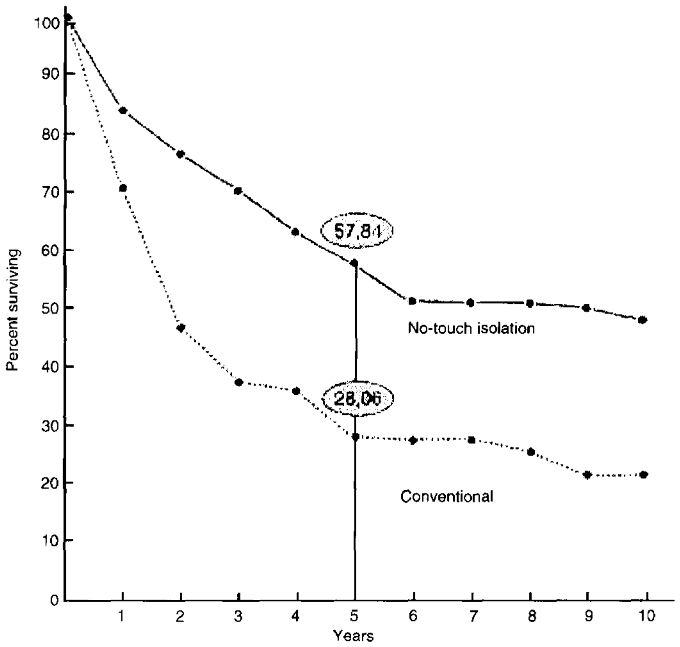

Fig. 2. The comparison of Turnbull of the 'no-touch isolation' technique vs. conventional (with permission Ann Surg 1967; 166(3): 420–427).

nodes removed lymphatic spread. Turnbull reported improved survival rates following colonic cancer resection and later also for rectal cancer, however, this was not a randomised trial (Fig. 2, [29]).

Current standard resections are shown in Table 2. The treatment of colonic tumours that invade adjacent organs is preferably multivisceral en bloc resection. Except from individual experience, there are no data supporting a neoadjuvant treatment initiative.

Most of the above concepts have been supported by subsequent investigations. Rinsing of the rectal stump prior to construction of the anastomosis has decreased the number of intraluminal recurrences [30,31]. In contrast, extended locoregional lymphatic dissection has not improved survival in small randomised trials although local and regional recurrence rates have decreased [32–35]. Any unnecessary manipulation of the tumour during resection must be avoided and to adhere to the rules of Turnbull's philosophy is a minor effort given that it may have a major impact on intraoperative dissemination of tumour cells (Table 3). This policy should be followed as a standard whether colonic resection is performed by open laparotomy or as a laparoscopical procedure (see also p. S180, "The surgeon as a prognostic factor").

In *rectal cancer*, pathological studies over the past 20 years have shown that distal intramural spread is rarely greater than 1 cm and it is safe to reduce the minimum margin of clearance from 5 to 2 cm [38,39]. However, knowledge about the circumferential spread [40] and the landmark publication (by Heald in 1982) referring to "the mesorectum as the clue to pelvic recurrence" (see ref. [41]), represented major steps towards the development of adequate resection techniques for lymphatic clearance. By following this concept, the incidence of local recurrences can be less than 5% [42] and total mesorectal excision (TME) today is standard surgery for cancer

Table 2
Extent of colonic resection and lymphatic clearance depending on tumour location

Tumour location	Standard operation	Lymphatic clearance
Caecum/ascending colon	right hemicolectomy	ileocolic + right colonic artery
Hepatic flexure/right transverse colon	extended right hemicolectomy	ileocolic + right colonic artery + mid colic, right gastroepiploic
Left transverse/splenic flexure	extended left hemicolectomy	mid + left colic artery
Descending colon/upper sigmoid	left hemicolectomy	inferior mesenteric artery
Mid + distal sigmoid	sigmoid resection	left colic artery

Table 3
Comparison of outcome elements in patients undergoing resection for rectal cancer dependent on whether or not disruption of the tumour specimen took place intraoperatively (adopted from [36,37])

	No signs of disruption	Disruption/cell spillage of the resection specimen	*P* value
Total group (*n*)	718	53	
5-Year survival	70 ± 5%	44 ± 17%	<0.01
pT2N0M0 (*n*)	201	15	
5-Year survival	92 ± 0.7%	61 ± 30%	<0.05
LRR rate	12%	29%	<0.05

LRR, local recurrence rate

of the lower and mid-rectum. While carrying out TME, it is important that the hypogastric plexus, as well as the pelvic nerves, are protected in order to try to avoid bladder, sexual and defecation problems postoperatively (see p. S178). The anastomosis is usually located 2–3 cm above the dentate line and the rectal reservoir is no longer present. Operative technique differs according to the way that the mesorectum is first identified and its vascular pedicle is then followed upward to the origin of the superior rectal artery from the main stem of the inferior mesenteric artery. A general recommendation cannot be given whether a defunctioning stoma (preferably ileostomy vs. colostomy) should be used to protect deep colo-rectal or colo-anal anastomoses for 6 to 8 weeks. In patients with preoperative radio- (chemo-) therapy it is clearly advisable. If an ileostomy is chosen, one should bear in mind that high fluid loss may occur which is of particular interest in patients undergoing postoperative systemic chemotherapy. In these patients, increased attention must be paid to stoma function and hydration status. In contrast to suggestions published earlier, there seems to be no influence on the rate of anastomotic leakages or recurrences according to whether the anastomosis is handsewn (even transanally) or performed by the double-stapling method [43,44], if it is performed by an experienced surgeon.

Surgery within combined modality therapy concepts

In locally advanced rectal cancer, there is a clear indication for combined modality therapy. There is a consensus and standard that adjuvant postoperative radiotherapy (combined with chemotherapy) should be applied in patients with stage III tumours (pT1-3 N+ M0). This treatment is recommended, on a weaker basis, also to patients with a pT3/4 N0 (0/>12 nodes examined) tumour (see the chapter in this book by Glimelius).

Results of a study comparing pre- and postoperative radiotherapy, however, suggested that preoperative radiotherapy was more effective than postoperative radiotherapy in preventing local recurrence [45]. A randomised trial has also demonstrated that preoperative radiotherapy improves survival [46].

A confounding factor in assessing the benefit of adjuvant radiotherapy has been the increasing use of more radical surgical techniques, particularly TME. It has been argued that the use of this technique renders the need for adjuvant radiotherapy obsolete. The most recently completed Dutch and Swedish trial randomly compared TME-surgery for rectal cancer alone vs. 5 × 5 Gy preoperative radiotherapy followed by TME (radiotherapy + TME) in 1861 patients [47]. Patients eligible for the study had tumours located within 15 cm above the anal verge and tumours that could not be removed by local excision. Patients with fixed tumours were excluded and surgery had to be performed within 10 days from the first day of irradiation. With a median follow-up of two years, the overall survival rate is 81.6% in the TME group and 81.9% in the radiotherapy + TME group. The risk of distant metastases was also not significantly different. However, the incidence of local recurrence was significantly different with 2.5% in the radiotherapy + TME group vs. 8.3% in the TME alone group (overall local recurrence rate 5.4%, $P < 0.0001$, hazard ratio of 3.6). This effect could be demonstrated for all TNM stages, but only reached significance in stage II ($P = 0.004$) and stage III ($P = 0.0001$) patients. With respect to the location of the tumour, a significant influence of radiotherapy could be demonstrated only in tumours located 0–5 cm ($P = 0.043$) and 5–10 cm ($P = 0.0001$), whereas in tumours beyond 10 cm there was no statistically significant effect ($P = 0.18$). In a multivariate analysis, allocation to treatment group ($P < 0.0001$), TNM stage ($P < 0.001$), and tumour location ($P = 0.03$) were independent predictors of local recurrence. Thus, the introduction of TME led to a major decrease in the local recurrence rates, however, preoperative radiotherapy still adds to the local control in operable rectal cancers. This trial is important as the results have been obtained in a multicentre setting with extensive surgical quality control and instructions to achieve standardised operative techniques as much as possible.

Postoperative morbidity in this trial showed that there was a slightly increased blood loss in the radio-

Table 4
Problems encountered with surgical procedures following preoperative radio- and/or chemotherapy

Positive effects of preoperative radio- and/or chemotherapy (neoadjuvant concept)
- Tumour shrinkage (downstaging) improves resectability
- May sterilise the tumour boundaries
- May prevent tumour cell spillage during operation
- May increase the resection rate with clear margins (R0-resection)

Problems associated with patients operated upon after upfront radio-chemotherapy (emergency and elective operations)
- Anaemia and impaired bone marrow reserves
- Neutropenia and lymphocytopenia
- Changes in microbial flora (fungal overgrowth in bacteria-contaminated organs due to the use of antibiotics)
- Translocation of bacteria is facilitated (enterocolitis)

Negative effects on surgical procedures
- Extent of tumour boundaries sometimes more difficult to assess
- Rate of anastomotic leakage in hollow organs may be increased (e.g. rectal or oesophageal cancer)
- Postoperative wound healing problems

therapy + TME group, and significantly more perineal complication after abdomino-perineal excision 26% vs 18% ($P < 0.045$) confirming the results of the randomised trial of pre- vs. postoperative radiotherapy [48]. No significant difference could be observed in the rate of clinically overt leakages (11% after TME vs. 10% after radiotherapy + TME, non-significant). Operative mortality was 3.2% in the TME group and 3.6% in the radiotherapy + TME group.

With adequate technique and understanding of the mechanisms of combined modality therapy, radiotherapy does not necessarily adversely influence the surgical treatment (see Table 4). However, it should be noted that patients with locally advanced tumours were not randomised as preoperative, short-term treatment is unable to induce significant downstaging [49]. In these patients (see Fig. 1) preoperative treatment should consist of 40 to 50 Gy of radiotherapy over four to five weeks combined with chemotherapy or even locoregional hyperthermia [50] to improve the extent of downstaging.

Reconstructive procedures

Low anterior resection has become the treatment of choice not only in tumours located in the mid-third of the rectum, but also in the lower third if histological and staging features of the tumours are fulfilled and TME is performed. However, end-to-end colo-anal anastomosis might be followed by urgent

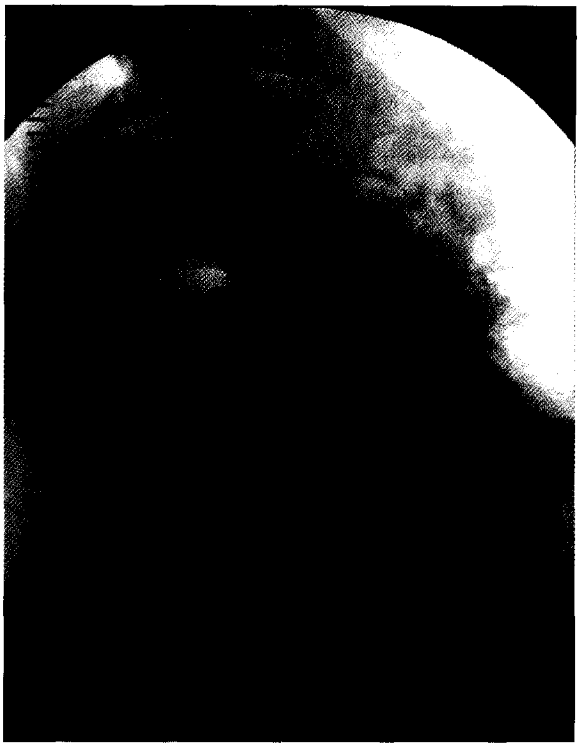

Fig. 3. Filling capacity of a colonic J-pouch after low anterior resection documented by barium enema.

bowel movements and often incontinence. As a consequence, the colo-anal pouch was developed to overcome the loss of the rectal ampulla as a stool reservoir. Beyond the functional advantage of a J-shaped colonic pouch, introduced by Lazorthes in 1986 [51], a technical advantage was postulated as the anastomosis is formed not with the end-part of the colon, but as a side-to-end anastomosis with better blood flow. Following randomised trials, authors reported that the most devastating functional problem of fluid or semisolid stool consistence is improved by the construction of the colonic reservoir [52–54] (Fig. 3). The pouch can be performed handsewn or using the double stapling technique and there are no clear-cut data favouring one of the approaches. The incidence of fistulas and pelvic abscesses is not increased, nor is the operative procedure significantly prolonged. Oncological results were reported not to be compromised [55]. Another interesting approach is the use of the ileocecal segment to replace the rectum between the descending colon and the dentate line following resection for low rectal cancer [56,57]. This procedure is not widely used, but the caecum-reservoir as a neorectum uses an intact neurovascular colonic segment, and may provide excellent defecation quality.

Approximately 25% of patients with low rectal cancer still undergo abdominal perineal excision and may be candidates for sphincter reconstruction. Numerous procedures have been proposed during the past decades, starting from metallic and magnetic implants, seromuscular spiral cuffs taken from the descending colon, or electrostimulated gracilis neosphincter [58], an overview is given by Madoff et al. [59]. The latter technique has a surgical experience of more than 15 years, however, it has not been widely accepted. It should only be carried out at very experienced centres or under the guidance of an experienced surgeon. Complication rates are rather high [60] and it can be expected that approximately two-thirds to three-fourths of the patients may become continent. Any factors of high risk of locoregional recurrence (lymphangiosis, venous invasion, high grade) should be seen as a contraindication for the procedure on the grounds of the lack of a long life expectancy for the patients, and postoperative radiotherapy should not be required as a part of the treatment programme.

Laparoscopic colorectal surgery

Recently, there has been much interest directed to the removal of colorectal cancer by a laparoscopical technique. Benefits were claimed in comparison with the open technique. The initial counter argument of limited radicality demonstrated by a low number of lymph nodes cannot be maintained. Operation time may still be a little prolonged, but further advances in the technique and technical aids (ultrasonic knife) may solve this problem [61]. The most important question concerns the risk of trocar (port site) implantation metastases observed even in early stage cancers. The true incidence remains unclear [62–64] since only clinically overt metastases are documented. The oncological outcome of the only prospectively documented series (although not randomised) seems to be comparable [65,66]. Further long-term follow-up and more randomised trials are required to determine the role of laparoscopical surgery in colorectal cancer.

Quality control in surgery for colorectal cancer

Obviously, resectability rate, proportion of patients resected with clear margins (R0-resection), and the rate of monobloc resections for T4-tumours can be used to assess quality control (Table 5). Other criteria include the proportion of patients receiving appropriate adjuvant/neoadjuvant treatment and the rate of patients being treated within clinical trials. Examination of the resected specimen allows analysis of the completeness of a resection that claims to be radical (R0-resection) [39]. The analysis of the resected specimen does not depend only on the extent of clearance by the surgeon, but also on the ability of the pathologist to assess the lymph nodes and margins. Incomplete surgical removal will leave the tumour behind. Inadequate examination by the pathologist will result in a false-negative assessment of the lymph node status. This can lead to poor survival in patients wrongly classified as node-negative, so that stage-adjusted survival rates with adequate surgery are compromised by inadequate pathology. Patients with false-negative nodes may not receive adjuvant treatment. These technical details and histopathological findings may serve as surrogate endpoints predicting late outcome [67].

Table 5
Objective measures for quality control in colorectal cancer surgery

- Assessing the resection specimen for en bloc removal, completeness and margins
- Counting nodes within the lymphatic drainage area to assess adequacy of clearance
- Proportion of patients with positive nodes (assesses also accuracy of pathology)
- Proportion of patients with sphincter-saving resection
- Incidence of local recurrence
- Incidence and type of postoperative morbidity (procedure-related, general complications)
- Postoperative (hospital) mortality
- Analysis of functional outcome (defecation, sexual function)
- Quality of life

The *incidence and type of postoperative morbidity and mortality* represent further criteria of surgical quality. Subsequent length of in-hospital stay or stay on an intensive care unit (ICU) ward are influenced by the age of the patients and whether it was an emergency versus elective operation, as well as by tumour and patient-related factors, and surgical skill. Significant differences between hospitals and surgeons regarding complication rates for colorectal cancer surgery have been detected. The rate of non-surgical complications ranged from 7% to 22% and the rate of surgical complications from 3% to 20%. The relative risk for different institutions in a multicentre German analysis involving both university and district hospitals [68] ranged from 0.54 to 2.29. A similar analysis from the U.K. showed a variation in R0-resection rates among surgeons from 40% to 76%, a rate of anastomotic leakages from 0% to 25%, and a range of postoperative mortality from 8% to 30%. The corresponding differences in survival at 10 years in patients who underwent a curative resection varied from 20% to 63% [69].

Prominent in the above studies were differences in the *local recurrence rates* and in disease-free survival. The incidence of local recurrence is almost always related to the quality of the surgical procedure (see above). Disruption of the specimen, intraoperative tumour cell spillage, and implantation of metastases also indicate surgeon-related factors (Table 3). In a study of seven German hospitals, the rate of recurrence ranged from 5% to 25% and the 5-year survival (stage corrected) from 48% to 70%. The recurrence rate among individual surgeons after taking into account the identified risk factors varied from 0.56 to 2.03 for curative (R0) resections [67].

The surgeon as a prognostic factor

Since the early 1980s, there have been reports of an inter-surgeon variability in the treatment results, particularly in the incidence of local recurrence, disease-specific and overall survival [69–71]. Comparisons have been made between surgical centres with respect to survival and local recurrence rates. A Canadian study of 680 patients involving 54 surgeons showed that surgeons performing less than 20 rectal cancer resections had a significantly higher risk of tumour cell spillage, tumour rupture and local recurrence than those performing higher numbers of operations per year [72]. This was the second most significant factor for local recurrence and translated into differences in disease-specific survival of the patients. Multivariate analysis with disease-specific mortality, as an outcome variable, showed the extent of training followed by the stage of the disease, rectal perforation and vascular or neural invasion of the tumour were the four most important factors. Very similar results were reported from the UK [69].

There has been much discussion of the influence of volume of work for the outcome of treatment for patients [73]. It has been shown for rectal cancer that the number of operations performed per year significantly influences operative mortality [74–76]. For colorectal cancer, there was a relationship between hospital volume and late survival in American university centres, New York hospitals, and those in the U.K., [77,78]. It is sometimes difficult to separate the influence of hospital and surgeon workload as there are cultural differences in providing medical services which tend to be surgeon/consultant directed in the U.S. in comparison to hospital-directed scenarios in other countries.

Other analyses for surgery-related factors have evaluated workload, subspeciality training and experience of surgeons (trainees vs. consultants). In some studies, neither consultant workload or hospital throughput were identified as independently influencing survival [76]. There is also evidence that properly supervised trainees can resect colorectal cancer without compromising long-term survival [79]. An analysis from Canada demonstrated that neither high workload or subspeciality training alone resulted in the best results, but the combination of training and experience yielded the best disease-free survival and lowest local recurrence rates [72].

The German analysis has shown that extensive personal experience with more than 50 colorectal resections per year may still be associated with a high local recurrence rate — some surgeons may learn from experience, while others do not! Personal attitude, subspeciality training, and commitment together with a thorough quality control programme are the most important factors to optimise surgeon-related contributions to disease-specific outcome. In the surgical training programme in Stockholm, when the technique of TME was adopted, a drop in the local recurrence rate from 15% to 6% occurred and cancer-related death improved from 16% to 9% [80].

Postoperative care and follow-up

Postoperative follow-up intends to serve two aims:

- Management of post-surgical problems and
- Early detection of recurrent disease or a second primary tumour

Auditing and providing quality control of the surgical procedure are also important. It must be noted, however, that if early detection of a recurrent tumour does not occur at the stage of a curable lesion "anxiety is needlessly produced by premature knowledge of the presence of a fatal disease" [81].

In patients treated with curative intent for a primary colorectal cancer, postoperative follow-up should be risk-adapted. Thorough clinical investigation and exploration of the patients in terms of bowel habits and sexual function following surgery for rectosigmoid cancer is important to assess the quality of life and is often helpful to identify recurrent tumours.

Four prospectively randomised trials have been conducted comparing more extensive follow-up programmes with a policy based on clinical examination only, but could not demonstrate superiority in terms of survival due to the lack of statistical power [82–85]. A meta-analysis demonstrated a 2.5 times higher rate of operations for recurrence and an improvement of survival by 16% in those patients with extensive follow-up, but is hampered by analysing data from a non-randomised series [86].

Colonoscopy at one year, and if negative every two to three years, seems reasonable to detect second primary or polyps. Patients with HNPCC should be examined at least once a year. In cases of preoperative elevated serum CEA, postoperative control helps to assure the completeness of tumour removal, and following this marker may be helpful in the early detection of recurrence. It does not make sense to routinely monitor serum CEA levels in patients with preoperative negative values. Abdominal ultrasound is recommended at three-monthly intervals during the first two postoperative years and six-monthly intervals thereafter to detect metastatic disease, whereas X-ray of the chest should be performed at six months postoperatively and yearly thereafter.

Following anterior resection, endoluminal ultrasound is the procedure of choice to detect local recurrences [87,88]. Sphincter manometry determining resting and squeezing pressure might be of value in exploring complaints of patients concerning defecation [89]. In patients undergoing preoperative radiochemotherapy for locally advanced rectal cancer, development of locoregional recurrences may be delayed beyond the second postoperative year.

Treatment of locoregional recurrence

Following resection of *cancer of the colon*, locoregional recurrences are reported with an incidence up to 15% [90,37] and predominantly develop following cancer of the transverse colon. Surgical resection, wherever possible, combined with chemo-and/or radiotherapy is the treatment of choice, however, recurrences often develop after resection of locally advanced tumours and all surrounding structures have already been removed at the operation for the primary. In these cases, extended, multivisceral procedures are indicated, if no distant metastases are detected and clear margins can be achieved. There are no data available using systemic chemotherapy under neoadjuvant conditions, although this maybe indicated on an individual basis. Bypass procedures are the method of choice in cases of intestinal obstruction under palliative conditions.

In *cancer of the sigmoid and rectum* different types of recurrences must be considered. Biological properties of the primary tumour contribute to locoregional recurrence together with the surgeons' technique and overall oncological strategy (Table 6). Adverse factors of the primary tumour are lymphatic, perineural, and venous invasion as well as mucinous type of adenocarcinoma and poor differentiation [91].

Table 6
Contributing factors to locoregional recurrence in colorectal cancer

Tumour biology
- Lymph node involvement (N+)
- Lymphangiosis carcinomatosa (L1)
- Perineural invasion
- Vessel invasion (V1/2)
- Poor differentiation (G3)
- Typing: mucinous adenocarcinoma

Surgical oncologist's strategy
- Postoperative chemotherapy given for stage III disease?
- Preoperative radiotherapy used for uT3 N+ tumour (clinical staging (CS) according to Mason 3 or 4 (fixed tumour frozen pelvis))?
- Postoperative radiotherapy performed for N+ tumour?

Technique of surgical resection
- Ligation of the bowel proximal and distal to the tumour
- Total mesorectal excision performed
- Washing of the rectal stump
- Intraoperative rupture of the tumour?

Intraoperative tumour cell spillage is often provoked by the surgeon's technique in handling the tumour and where methods to prevent the seeding of exfoliated cells have not been used ([31,36] Table 3). Adequate operative techniques such as TME, washing of the rectal stump, complete eradication of the lymphatic spread of the tumour are prerequisites for low recurrence rates. Distal margins of clearance alone are of less importance as we have learned from a thorough analysis of the pathological specimen (see paper by Quirke, in this book).

The incidence of local recurrences following rectal cancer are high if TME is not applied. A series of studies from the 1990's reported up to 25% of local recurrences following the treatment of colorectal cancer. Adopting the technique of TME as a teaching initiative, the local recurrence rates dropped from 15% to 6% and cancer-related deaths from 16% to 9% [80].

Several subtypes of recurrences requiring specific treatment can be discriminated:

Implantation metastases at sites of the laparotomy or perineal scar indicate tumour cell spillage during operation. Port site recurrences during laparoscopic surgery, as well as recurrence in a Hartmann's stump also belong to this category. Their true incidence remains unclear as only the positive (negative) cases are reported. However, this type of recurrence is the one to be treated most easily by extended surgical resection, combined with radiotherapy if local lymphatic invasion or narrow margins of clearance are achieved.

Regional lymphatic recurrence due to incomplete dissection of the lymphatic drainage area [92]. Following a left hemicolectomy or anterior resection, residual nodes at the inferior mesenteric artery or the superior rectal artery infiltrated by tumour represent a distinct entity. These recurrences are detected by rising CEA levels and not by endoscopy or endorectal ultrasound. Angiogram of the inferior mesenteric artery is helpful in establishing the diagnosis and low numbers of lymph nodes in the resection specimen of the primary tumour are further indicators. This type of recurrence might be resected with curative intent and can be prevented by keeping to the rules of oncological surgery with clearing the complete lymphatics of the respective tumour.

Local recurrences after adequate lymphatic clearance in the lower pelvis are often the consequence of aggressive tumour behaviour of high-grade lesions, including lymphatic and vessel invasive properties. If not already done during the treatment of the primary tumour, preoperative radiochemotherapy (40–50 Gy, combined with 5-fluorouracil (5-FU)/folinic acid) should be applied prior to any attempt to resect the recurrence. Following anterior resection, maintaining continence is impossible in the majority of the cases. If a curative attempt is followed, pelvic exenteration is advisable, as it offers the only chance to resect the former operation area *en bloc* by entering beyond the endopelvic fascia.

Locoregional recurrence in the lower pelvis following abdomino-perineal excision can be approached with curative intent only in rare cases. Usually, the tumour is fixed to the sacrum and the patients complain of pain when sitting, representing the leading and pathognomonic sign of recurrence. An approach for curative resection almost always includes partial sacrectomy and results in major morbidity. It should be performed if no loss of stability to the pelvis is encountered. In general, this implies direct invasion of the sacrum at or below the level of S3. Those procedures should only be performed in experienced centres as major blood loss, extended operation time and plastic reconstructive procedures (preferably rectus abdominis myocutaneous flap) may be required for wound closure.

Additional local radiotherapy by intraoperative radiotherapy (IORT) or brachytherapy should be considered in any of these scenarios to improve local control.

Treatment results for locoregional recurrence of colorectal cancer are generally poor. At best, regional lymphatic metastases and implantation metastases might be resected for cure in 40 to 60% of the patients [92]. However, recurrences in the pelvis can be approached with curative intent in approximately 20% of the patients resulting in a median disease-free survival of 25 to 37 months [93–95]. All resections for recurrence need a combined treatment effort preoperatively, intraoperatively, and postoperatively to bring together chemotherapy, radiotherapy (particularly brachytherapy or IORT), and surgery.

Treatment of liver metastases

As already mentioned, 30% to 40% of the patients with primary colorectal cancer have distant metastases. Of these, 25–30% suffer from liver metastases as the only location. Depending on stage, grade, and size of the primary tumour another 15–25% of the patients develop liver metastases in the further course of disease. There are convincing data that liver resection in a well selected group of patients may result in long-term cure, even if multiple resections with longer intervals in between may be required. Approximately 20% of patients can be observed (not calculated) to be free from disease following liver resection for colorectal secondaries at 5 years. Of these, 91% can be expected to be free from disease also at ten years (Registry of Hepatic Metastases). On the other hand, thorough analyses demonstrated that there are numerous patients undergoing liver resection without a chance for cure for a resected lesion that was supposed to be solitary represented the tip of an iceberg [96]. No prospective, randomised studies have been performed to answer the question whether preoperative chemotherapy improves survival in comparison to liver resection alone.

The risk-score concept initially published in 1991 [97] and later on evaluated on a large number of patients by Nordlinger et al. ([98], Table 7) seems reasonable from a scientific and clinical point of view and has been proven by data. Besides stage and grade of the primary tumour, size, and number, and distribution of the metastases also the time interval between detection of the metastases and resection of the primary tumour, as well as age of the patient, contribute to the scoring system. Dependent on the score, patients can be allocated to prognostic groups representing clearly different expected survival rates.

Table 7
Criteria of liver metastases to be classified as 'good risk' (left) or 'bad risk' according to Nordlinger [98]

Primary tumour:	local invasion	T1/2 vs. T3/4
	Nodal status	N− vs. N+
Number of metastases		1–3 vs. >4
Time interval to the primary		> or <2 years
Largest metastasis		< or >5 cm
Resection margin		> or <1 cm
Age		< or >60 years

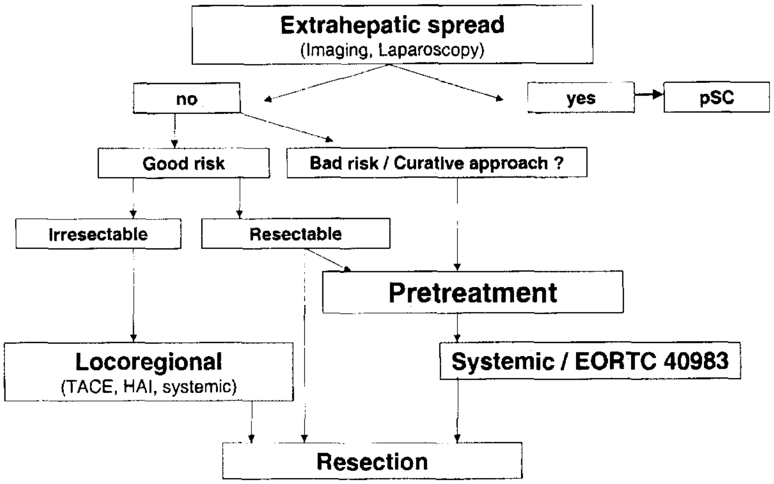

Fig. 4. An algorithm for the decision of surgical treatment for colorectal liver metastases (pSC = palliative systemic chemotherapy, HAI = hepatic arterial chemotherapy, TACE = transarterial chemoembolisation).

Interestingly, this concept was proven also for lung metastases of a different origin [99] and survival curves following resection are very similar to those obtained for colorectal liver metastases.

For clinical purposes, patients belonging to the 'good risk' group (stage I/II primary, long time interval to the liver secondaries, solitary lesion) should undergo resection if possible (see Fig. 4). Patients allocated to the 'bad risk' group clearly are candidates for upfront chemotherapy. Patients belonging to the intermediate group should be treated according to institutional preferences. As there are several publications on preoperative chemotherapy, whether systemically or intra-arterially, resulting in downstaging making irresectable liver metastases amenable to surgical removal, the concept of a neoadjuvant (preoperative) chemotherapy anteceding liver resection needs to be explored. In conjunction with the permanent working party on surgical oncology (CAO) of the German Surgical Society, the EORTC has initiated a trial (protocol no. 40983) evaluating the effect of six cycles of each preoperative and postoperative chemotherapy consisting of 5-FU/leucovorin and oxaliplatin (FOLFOX2) in comparison to surgical resection alone. As this trial requires 360 patients to be randomised within 3 years, to confirm the superiority of the multimodality concept by improving median disease-free survival from 16 to 22 months, it is highly recommended to include those patients into the trial (see Table 8).

Prior to indication for liver resection, extrahepatic tumour spread must be ruled out. Despite complete resection of extrahepatic tumour extension prognosis of these patients is extremely poor and most of the patients do not have a long-term profit from the procedure. Diagnostic laparoscopy revealed invasion of metastases to the diaphragm, lymph node metastases at the hepatoduodenal ligament or peritoneal carcinosis resulted in the skipping of the procedure in 39% and 43%, respectively, of the patients scheduled for liver resection [100,101]. Beyond extensive imaging procedures, preferably MRI with gadolinium-enhanced contrast, and computed tomography (CT)-scan of the chest and pelvis (in cases of a rectal primary cancer), laparoscopy should be applied whenever possible with respect to abdominal adhesion formation and incision lines. In the future, FDG-PET will probably be helpful in detecting extrahepatic tumour spread.

Regarding the technical aspects of liver resection, a margin of clearance of 10 mm of uninvolved tissue is enough. It is generally accepted that 3 to 4 liver

Table 8
Major inclusion criteria for patients to be treated within the EORTC 40983 protocol (pre- and postoperative chemotherapy plus liver resection for colorectal secondaries)

- Liver metastases need to be resectable according to local policy
- Metachronous metastases without extraheptic spread after R0 resection of the primary tumour
- Synchronous metastases with the primary tumour resected at least one month prior to study entry
- Primary colorectal cancer, exclusively metastatic to the liver in patients who can be subjected to 3 to 4 months delay of tumour resection
- Age 18 to 80 years
- No prior systemic chemotherapy for advanced disease
- Adjuvant chemotherapy for the primary tumour allowed if no oxaliplatin was used

metastases represent the borderline of a reasonable indication for resection. Otherwise, systemic chemotherapy should be preferred. In solitary, large liver metastases, not amenable to surgical resection preoperative intra-arterial chemotherapy or chemoembolisation may be of value in downstaging the lesion and facilitating resection. In a series of 14 patients, volume expansion of the remaining liver lobe by 25% to 54% could be achieved following portal venous embolisation with histoacryl and lipiodol intended to increase the residual, well-functioning liver parenchyma postoperatively [102]. Elias et al. reported that following intra-arterial chemotherapy, 14 out of 239 patients (5.9%) could be downstaged i.e. a lesion previously classified as irresectable was now resectable [103].

More than 90% of the patients with liver metastases present with elevated CEA levels. Pre- vs. postoperative levels of CEA is an easy tool to monitor the completeness of resection [104].

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