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European rectal cancer consensus

## Multidisciplinary Rectal Cancer Management: 2nd European Rectal Cancer Consensus Conference (EURECA-CC2)

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## ABSTRACT

**Background and purpose:** During the first decade of the 21st century a number of important European randomized studies were published. In order to help shape clinical practice based on best scientific evidence from the literature, the International Conference on 'Multidisciplinary Rectal Cancer Treatment: Looking for an European Consensus' (EURECA-CC2) was organized in Italy under the endorsement of European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), and European Society of Therapeutic Radiation Oncology (ESTRO).

**Methods:** Consensus was achieved using the Delphi method. The document was available to all Committee members as a web-based document customized for the consensus process. Eight chapters were identified: epidemiology, diagnostics, pathology, surgery, radiotherapy and chemotherapy, treatment toxicity and quality of life, follow-up, and research questions. Each chapter was subdivided by a topic, and a series of statements were developed. Each member commented and voted, sentence by sentence thrice. Sentences upon which an agreement was not reached after voting round # 2 were openly debated during a Consensus Conference in Perugia (Italy) from 11 December to 13 December 2008. A hand-held televoting system collected the opinions of both the Committee members and the audience after each debate. The Executive Committee scored percentage consensus based on three categories: "large consensus", "moderate consensus", and "minimum consensus".

**Results:** The total number of the voted sentences was 207. Of the 207, 86% achieved large consensus, 13% achieved moderate consensus, and only 3 (1%) resulted in minimum consensus. No statement was disagreed by more than 50% of the members. All chapters were voted on by at least 75% of the members, and the majority was voted on by >85%.

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**Conclusions:** This Consensus Conference represents an expertise opinion process that may help shape future programs, investigational protocols, and guidelines for staging and treatment of rectal cancer throughout Europe.

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## Background

Although surgery remains the most important treatment of rectal cancer, the management of this disease has evolved to become more multidisciplinary. Multidisciplinary management is the preferred approach and offers the best clinical outcome [1].

During the first decade of the 21st century a number of important European randomized studies were published. They had examined a variety of adjuvant approaches and most had required the use of Total Mesorectal Excision (TME). In addition, advances in both pathology and imaging have further contributed to the multidisciplinary management [1].

In order to help shape clinical practice based on best scientific evidence from the literature, the International Conference on 'Multidisciplinary Rectal Cancer Treatment: Looking for an European Consensus' (EURECA-CC2) was organized in Italy under the endorsement of European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), and European Society of Therapeutic Radiation Oncology (ESTRO). The goal of this Consensus Conference was to help shape future programs, investigational protocols, and guidelines for staging and treatment of rectal cancer throughout Europe.

## Methodology

The Departments of Radiotherapy of the Catholic University of Rome and the University of Perugia, which organized the first Consensus Conference and are responsible for the development of an ESTRO Multidisciplinary Teaching Course managed with ESSO and ESMO organized the conference [1,2]. The members of the departments contacted the three European Societies for their participation and endorsement. The Executive Committee included two delegates from each of the three societies, two from the journal *Radiotherapy and Oncology*, and a radiologist, epidemiologist, and pathologist who participated in the multidisciplinary ESTRO teaching course.

The Executive Committee then selected, based on majority vote, the participants for the Scientific Committee from experts who were involved in the major European published trials. In total, 8 surgical oncologists, 8 radiation oncologists, 6 medical oncologists, 3 diagnostic radiologists, 3 pathologists, 1 epidemiologist, 1 representative from Central Europe, 1 representative from the EORTC, and the Editor of *Radiotherapy and Oncology* were selected for the Scientific Committee.

Consensus was achieved using the Delphi method [3]. Version 1 was created by the Executive Committee. Eight chapters were identified: epidemiology, diagnostics, pathology, surgery, radiotherapy and chemotherapy, treatment toxicity and quality of life, follow-up, and research questions. Each chapter was subdivided by a topic, and a series of statements were developed.

The document was available to all the Committee members as a web-based document customized for the consensus process. Each member commented and voted, sentence by sentence. In addition, references to each sentence were presented and the members were able to add additional ones. The outcome of each vote (percentage of agreement, percentage of disagreement, and new comments and references) was available to each member prior to the next vote.

Voting round # 1 took place between 24 September and 20 October 2008. The Executive Committee reviewed the suggestions of the experts and voting round # 2 took place from 10 November to 1 December 2008. Voting categories included: agree as is, reject, ab-

stain, or declare that he or she does not have sufficient knowledge to give an opinion. A vote of "abstain" was scored as moderate disagreement and the overall denominator was not changed. A vote of "insufficient knowledge" resulted in a reduction of the denominator by one thereby giving more weight to the vote of the other experts. All the members, regardless of expertise, were asked to vote on all chapters and sentences. At any point in the process the members could submit their comments or add a new reference.

During voting round # 2, all the members could view the percentage ratings and comments from voting round # 1. They were thus able to take into account the opinion of the other members before voting. The Executive Committee scored percentage consensus based on two categories: (1) If no members disagreed and the percentage of agreement was greater than 80%, "large consensus" was achieved, if the percentage of agreement was 71–80% "moderate consensus" was achieved, and if the percentage of agreement was 51–70%, "minimum consensus" was achieved. (2) If one member or more members disagreed and the percentage of agreement was greater than 95%, "large consensus" was achieved, if the percentage of agreement was 75–94% "moderate consensus" was achieved, and if the percentage of agreement was 51–74% "minimum consensus" was achieved.

Voting round # 3 took place during the conference in Perugia (Italy) from 11 December to 13 December 2008. The meeting was open to everyone interested in the topic. Sentences upon which an agreement was reached after voting round # 2 were openly debated by attendees at each session and the audience had the opportunity to ask further questions. A hand-held televoting system collected the opinions of both the members and the audience after each debate.

Following the conclusion of the Perugia meeting voting round # 4 took place from 20 January to 10 February 2009. The final text was reviewed and collated by two different experts (B.G. and B.M.) without changing the outcome of the votes.

The total number of the voted sentences was 207. Of the 207, 86% achieved large consensus, 13% achieved moderate consensus, and only 3 (1%) resulted in minimum consensus. The sentences with moderate or minimum consensus are identified in the text. All chapters were voted on by at least 75% of the members, and the majority was voted on by >85%.

## Epidemiology

Colorectal cancer (CRC) is the third most frequent cancer in both sexes in Europe, after prostate and breast cancers. It has been estimated that 163,100 males and 134,100 females were diagnosed with CRC during 2006 in the 25 countries of the European Union [4], representing 13% of all cancer cases. Approximately 30% of all CRCs are diagnosed in the rectum, which includes 49,000 males and 40,000 females in 2006. A decreasing trend in the age-adjusted incidence was observed in the last decade in the US, and in the European countries the incidence is stable or decreasing in most cancer registries.

Survival from CRC has been estimated for most European countries based on population cancer registry data in the EURO CARE project, covering incident cases from 1995 to 1999 and followed up through December 2003. The relative survival of CRC was 53.5% in both sexes, increasing from 49.3% in the period 1990–1994 [5]. An important variability between countries was observed however, the lowest relative survival being observed in Poland

(38.8%) and the Czech Republic (43.2%) whereas the highest was observed in Switzerland (59.7%), Norway and Sweden (58.3%). Intermediate values were seen in Spain (52.5%) and the UK (50.6–51.8%). Differences in survival were explained to a large extent by differences in stage at diagnosis. Cancer of the rectum has a prognosis that is similar to that of cancer of the colon, although in the countries where surgery has been centralised (Sweden and Norway) rectal cancer now has a better prognosis.

## Risk factors

### Diet

The key risk factors for CRC throughout the world are dietary (meat, fish, fibre, fat, folate, calcium and selenium), physical exercise, obesity and alcohol, as well as some medical therapies such as Non-Steroidal Anti-inflammatory Drugs (NSAIDs), Hormone Replacement Therapy (HRT), statins and oral contraceptives, and other medical conditions (inflammatory bowel diseases or diabetes), although inconsistencies in the studies associating these factors with the disease exist.

Red and processed meat significantly increases the risk of rectal cancer (RR = 1.65 95% CI 1.05:2.62), as well the protective role of fish was also observed, with a RR of 0.41 (95% CI 0.17:0.97) [6].

Calcium and milk intake (>250 g/day of milk) may be protective for rectal cancer (RR = 0.80; 95% CI 0.66:0.96) as well as for colon cancer [7].

Alcohol intake (of more than 30 g/day) is associated with a slightly increased risk of rectal cancer (OR: 1.42; 95% CI 1.07:1.88) and is chiefly associated with beer and wine [8].

### Genetic

There is a proportion of CRCs (around 5–10%) with hereditary susceptibility, 1–2% of them are inherited in an autosomal dominant manner. The most frequent of these are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome, the latter being more frequent in the proximal colon.

A majority of CRC cases (between 75% and 85%) are sporadic. The remainders are diagnosed in patients with first degree family relatives who are also affected by colorectal cancer. Those with one first degree relative have a twofold greater risk of developing bowel cancer than the general population.

## Prevention

### Chemoprevention

The protective role of aspirin and NSAIDs for both adenomas and CRC has to be balanced with the adverse effects of these drugs. Furthermore, the mechanism of action is unclear and currently there is no clear recommendation that they should be used for chemoprevention. The relationship of statins and CRC risk and their potential protective role have been examined. However, a systematic review and meta-analysis did not find a significant association [9].

The use of oral contraceptives was shown to exert a protective effect in rectal cancer (OR: 0.74; 95% CI 0.65:0.83) and in colon cancer as reported in a meta-analysis of cohort and case-control studies [10].

### Screening

Screening for CRC is effective in reducing the mortality risk among the screened population. In a meta-analysis of randomized

trials using faecal occult blood testing, a reduction of 16% in CRC mortality was observed (95% CI 7:23%) [11].

Other screening tests, such as colonoscopy and sigmoidoscopy, have been proposed and trials are underway to test their efficacy. Publication of these results will help to define the best strategy for screening for this cancer.

## Diagnostics

There are many different imaging modalities that are suitable for rectal cancer staging, tumour location, and restaging but not all of them have the same accuracy for each indication.

### T stage

#### cT1 vs cT2

With a moderate consensus, endorectal ultrasound (EUS) is considered the most accurate imaging modality for the assessment of tumour penetration into the rectal wall [12], even if, at times, it is difficult to determine the depth of invasion in large villous lesions.

For assessing the depth of tumour growth in the bowel wall EUS has an overall accuracy between 69% and 97% [12]. The highest accuracy is obtained in expert EUS centers. When EUS is performed in general clinical setting the accuracy significantly drops [13,14].

EUS cannot be reliably used in patients with high or stenosing tumours [15].

Endorectal MRI can be considered as accurate as EUS for staging superficial tumours as shown by comparative studies between the two endoluminal techniques. While the endorectal MRI allows an objective evaluation of the imaging also in high located or stenosing cancers, and is less observer-dependent than EUS. The endorectal MRI is more expensive, technically more demanding for the MR unit and less comfortable for patients. Therefore, investigation of superficial tumours is preferred with EUS in expert centers, even if the number of studies is limited [16].

Usually, the aim of these examinations is not to distinguish between cT1 and cT2 lesions but is restricted to cT1 sm1/sm2 and sm3 evaluation. Sm3 and T2 lesions require the same treatment. Most sm1 and sm2 lesions are removed at colonoscopy prior to staging, and subsequent management is often determined by histopathology and not by EUS or MRI.

Phased array MRI and multispiral CTs are not reliable in the differentiation between T1 and T2 lesions [17,19].

#### cT2 vs cT3

With a moderate consensus, endorectal MRI can be considered as accurate as EUS for differentiation of superficial (cT1 and/or cT2) rectal tumours and cT3.

Phased array MRI fails in the differentiation between T2 and borderline T3 lesions and overstaging is the main cause of errors. It is difficult to distinguish by MRI between desmoplasia without tumour cells (stage pT2) and desmoplasia with tumour cells (stage pT3). EUS has the same limitations [17,18].

Phased array MRI and multidetector CT seem to have an equal accuracy for staging advanced T3 tumours, although the number of available comparative studies is limited. CT cannot assess the depth of extramural spread as accurately as histology but MRI has been shown to be equivalent to histology in the measurement of extramural depth. Careful attention to technique and the use of high resolution sequences with scans planned perpendicular to anal canal and coronal scans to show the sphincter complex make MRI superior for lower third rectal tumours [18–20].

With a moderate consensus, new generation 16-slice spiral CT with optimal bolus timing and reconstruction in multiple planes can be considered to achieve high sensitivity and specificity for

the prediction of tumour penetration in the bowel wall, even if it appears not to be as accurate as MRI in the low rectum locations. The CT accuracy can be superior to EUS when the latter is performed in less expert EUS centers [21].

#### *cT3 vs cT4*

With a moderate consensus, EUS is considered not to be accurate in the assessment of local tumour extent in bulky T3 and T4 rectal cancer [12].

Multidetector 4–16-slice CT is accurate for staging the advanced T3 tumours in the middle and high rectum with especially a high NPV, at the expense of lower PPV. However, the accuracy decreases for tumours located in the lower rectum [18–20].

Phased array MRI is highly accurate in staging advanced rectal cancer, in the assessment of mesorectal fascia infiltration, and to distinguish cT3 from cT4 [17,18].

PET-CT does not add to the accuracy in evaluating the cT stage in advanced rectal cancer [22].

#### *Circumferential resection margin (CRM) evaluation*

##### *CRM+ vs CRM–*

With a moderate consensus, EUS and endorectal MRI are not considered accurate for mesorectal fascia evaluation.

Conventional CT is not helpful for predicting an involved resection margin [23].

Multidetector 4–16-slice CT appears promising for the prediction of a free circumferential resection margin, but not in low tumours, especially not in those located in the low anterior rectal wall [20].

Phased array MRI is highly accurate for the prediction of CRM positivity in routine clinical practice [17,18,24,25].

PET-CT is not reliable in the evaluation of an involved CRM [22,26].

Substaging of the cT3 group with MRI according to the depth of tumour extension into the mesorectal fat penetration of the tumour in the mesorectum is recommended [18,27].

#### *Tumour location evaluation*

##### *Low vs medium-high*

Although the digital examination is probably the most accurate for mid-rectal and lower rectal tumours, rigid proctoscopy is accurate in the evaluation of the tumour location. Flexible endoscopy is not always reliable in the definition of the tumour location.

EUS is very accurate in detecting sphincter infiltration, but is less accurate in the definition of tumour location. However, few studies have examined the staging of tumours with respect to the distance to the intersphincteric plane.

Multidetector row CT seems to be promising for the evaluation of the distance of the tumour to the anal sphincter [21].

Phased array MRI is accurate in measuring the distance between the anorectal junction and the distal part of the tumour; it is also accurate for determining the length of the tumour. Both endorectal MRI and phased array MRI are reliable in assessing sphincter infiltration. EUS is the preferred method but when it is not available the external phased array technique is recommended over an endoanal coil MR technique because it is easier for the patient to tolerate [17,28].

With a moderate consensus, there is still controversy regarding the definition of the extraperitoneal and intraperitoneal rectum by imaging, even if the external phased array MRI contributes to the identification of the peritoneum in the upper rectum [18].

Both endoanal MRI and phased array MRI are reliable in assessing sphincter infiltration. Sphincter infiltration can be accurately assessed by digital examination and/or EUS, but if an MRI is per-

formed sphincter infiltration is also accurately evaluated on MRI using an external phased array technique and is recommended above an endoanal coil MR technique. However, the number of available studies is limited [17,28].

#### *N stage*

##### *cN0 vs cN1–2*

With a moderate consensus it was agreed that identifying nodal disease is still a diagnostic problem for the radiologist. Nodes >8 mm are defined as malignant nodes on CT, MRI and EUS. In contrast, despite the identification of lymph nodes as small as 2–3 mm on modern planar imaging, reliable detection of nodal metastases is presently not possible, because CT, MRI and EUS all rely on size criteria for predicting nodal metastases [25].

EUS is considered slightly superior to non-contrast enhanced MRI and CT for nodal staging but the entire mesorectum cannot be explored. EUS-guided fine needle aspiration has been reported to be a very reliable method with accuracy up to 100%, but it is a cumbersome technique that has not gained widespread acceptance [25].

New generation multislice spiral CT cannot accurately distinguish between malignant and benign lymph nodes measuring <8 mm [29].

Size is not a good predictor for malignancy and should not be used for defining whether lymph nodes are involved or not. The most reliable method of positively identifying nodal metastases is based on morphological features such as the presence of mixed signal intensity within the lymph node and/or irregularity of the borders of the lymph node due to capsular penetration by malignancy. The overall accuracy is lower than other prognostic features that can be identified more reliably using high resolution MR scan techniques [30].

FDG-PET has shown disappointing results for N staging in rectal cancer, especially in the mesorectum in the presence of a bulky tumour [22].

#### *M stage*

##### *Detection of extrapelvic metastases*

Chest X-ray, abdominal CT or MRI is the minimum requirement in clinical rectal cancer staging.

Thoracic and abdomen CTs are recommended as part of the staging protocol to detect distant metastases, especially for the high risk rectal cancer [31].

For the characterisation of liver lesions, MRI is superior to helical CT and is recommended in equivocal liver lesions seen on CT. A meta-analysis has compared the sensitivity of CT, MRI and FDG-PET for detection of colorectal liver metastases on per-patient and per-lesion bases. FDG-PET had significantly higher sensitivity on a per-patient basis, but not on a per-lesion basis. Sensitivity, per-lesion basis, for MR imaging using liver-specific contrast agents was significantly superior to that for helical CT [32].

Bone scan and brain imaging are required for clinical symptoms only.

##### *Imaging after radio(chemo)therapy*

##### *Responders vs non-responders*

The detection of small clusters of residual tumour cells remains a problem and a complete remission after neoadjuvant chemoradiation cannot be reliably predicted with non-invasive imaging tools. Although EUS, CT and MRI can assess downsizing of the tumour, they are not accurate, especially when there is a fibrotic thickening of the rectal wall, in distinguishing between ypT0, ypT1, ypT2 and ypT3 tumours. The main source of error is overstaging.

With a moderate consensus it was agreed that reasonably high level of accuracy has been observed by phased array MRI when the endpoint is differentiating ypT0–2 vs ypT3. Although it could be useful for the surgeons to plan less extensive surgery, there is no solid evidence for this [33].

Many studies have reported a significant decrease of standardized uptake value (SUV) on postradiation FDG-PET in responders when compared to non-responders, but the clinical value of this information remains to be determined [34].

## Pathology

The pathologist can help save lives and improve clinical management by working with the multidisciplinary team. Pathologists contribute to the knowledge about prognosis given to the patient, the audit and learning processes of surgeons and radiologists, and the preoperative and postoperative treatment plans of the oncologists. They are also driving our understanding of the biology of the disease and possibly the prediction of the types of therapies that the patient might respond to [1].

### Handling of the specimen

#### Quality of routine pathology

Guidelines are important and there should be national or preferably international guidelines for the dissection and reporting of CRC. The Guidelines of the Royal College of Pathologists in the United Kingdom have gained widespread acceptance as the minimum standard for reporting this disease. They are available at <http://www.rcpath.org/index.asp?pageID=1153>.

The macroscopic examination of the specimen is critical and of prognostic significance. From this an understanding of the anatomy and its variability can be obtained: an appreciation of macroscopic features helps guide pathological analysis [35].

The anterior and posterior surfaces should be photographed to record any perforation and the plane of surgical dissection. The specimen is opened anteriorly except for the area of the tumour which is left intact to allow assessment of CRM involvement without distortion introduced by opening the bowel. The surgically created margin surfaces are painted with ink [36,37].

The specimen should be fixed in formalin for 72 h or longer. It should then be described and the tumour (including 2 cm below and above) should be thinly sliced (3–5 mm). Good fixation allows thinner slices to be taken and thus a better assessment of tumour spread. These slices should be photographed to document the plane of surgical dissection [36,37].

The distance of direct tumour spread outside the muscularis propria should be recorded and the area in which tumour spreads closest to the CRM should be identified macroscopically. Blocks should be taken from the area closest to the circumferential margin and any area where the tumour extends to within less than 3 mm from the margin. Other blocks should be taken to include at least 5 blocks of tumour to confirm the presence or absence of extramural venous invasion [36].

Accurate nodal staging is of critical importance for selecting patients for adjuvant therapies. Careful slicing of the mesorectal fat, visual inspection and palpation are recommended to find sufficient numbers of lymph nodes. Fat clearance techniques may improve the yield of lymph nodes. However their routine use cannot be recommended.

TNM and NICE guidelines recommend that at least 12 nodes should be harvested, even if after preoperative treatments it could be more difficult to find them. Current ASCO guidelines advise that in cases of less than 10 lymph nodes, patients should be classified as high risk TNM stage II and could be eligible for adjuvant therapy.

There is a negative correlation between the number of lymph nodes examined and local recurrence in stage II disease [38].

### TNM stage system

#### Classification system

With a moderate consensus it was agreed that the TNM stage has to follow the International Union Against Cancer (UICC), Geneva, Switzerland. The version of TNM used should be stated in any publication. Version 5 is the preferred option (TNM Classification of Malignant Tumours, Fifth Edition (1997) (<http://www.uicc.org>) over TNM versions 6 and 7 as they show marked interobserver variation in defining stage II and stage III [39].

### Evaluation of surgical margins

#### Circumferential resection margin

Surgeons identify margins that can be involved by tumour spread at a variety of sites. The most well known are the proximal and distal margins of a resection. An additional margin is the mesenteric margin where the surgeon devascularises the bowel. By far the most important margin is that created around the mesorectum (Circumferential Radial Margin = CRM). This margin is under threat by direct involvement but also by the incomplete removal of lymph nodes that lie just under the mesorectal fascia. Any small deviation from the correct surgical plane could enter tumour cell deposits, potentially compromising cure [1].

Close or positive CRM correlates with increased local recurrence rates and decreased survival by half: these data support the importance of clear surgical CRM [40].

There is a strong agreement that higher local recurrence rates, higher distant metastases rates and poorer survival are seen when the CRM is involved or less than 1 mm [39,40].

With a moderate consensus it was agreed that one group has reported higher local recurrence rates, higher distant metastases rates and lower survival when clearance is less than 2 mm rather than 1 mm [41]. Patients with less than 2 mm could be considered at higher risk, but more studies are needed to change this figure from 1 to 2 mm in routine practice.

### Staging after radio(chemo)therapy

#### The evaluation of tumour regression

There is good evidence that preoperative chemoradiotherapy is able to downstage rectal tumours. In approximately 8–30% of cases this can lead to complete disappearance of tumour cells. Variation in sampling protocols may explain some of the differences in the frequency of complete pathological response described in the literature. Recently, a protocol to classify a tumour having a complete pathological response has been recommended [42].

There are a number of suggested methods for assessing tumour regression after preoperative treatments. These are modifications of the scoring system developed by Mandard et al. for oesophageal carcinoma. Using similar grading systems the presence of very few or no tumour cells was associated with a much better outcome after therapy. It may be possible to simplify these into tumours that show an *excellent response*, i.e., no residual tumour cells, a *good response*, i.e., tumour cells that are difficult to be found microscopically or easily identifiable tumour cells and *no response* at all [43].

To declare a complete pathological response, initially at least 5 tissue blocks should be taken from the tumour site. If there is no tumour present in these, the whole tumour area should be blocked. If still no tumour is present, three levels should be cut from each tumour block. If still no tumour is present, there is a pathological complete response. The most practical subdivision for the grading

of tumour regression is: no response, signs of response, near complete response, and complete response [36].

#### *Certification of surgical quality*

##### *The evaluation of surgery quality*

The recording of the frequency of involvement of the surgical CRM is important for feedback to radiologists for accuracy of prediction as well as to the surgeon as an indicator of the prognosis for the patient and, at times, of the quality of surgery [40].

An assessment of the quality of specimen and of the surgical margins should be routinely made by the reporting pathologist [40].

The assessment of abdominoperineal excision specimens to measure the amount of tissue removed at the anorectal junction and to determine whether the levator muscle is included in the resection is strongly recommended. This allows an evaluation of the potentially exposed tumour in a similar way as for the mesorectum [44].

## **Surgery**

Loco-regional tumour control in rectal cancer surgery has changed dramatically during the past 10–15 years. This started with discussions of the value of more exact surgery and precise procedures following embryonic planes. The role of the main surgical procedures for early, intermediate and locally advanced lesions is examined [45].

#### *Early localized tumours*

Early tumours are neoplasms limited to the rectal wall (c/p T1–2 N0 M0). They represent 3–5% of rectal cancers, and include small, exophytic, mobile tumours without adverse pathologic factors (i.e., high grade, blood or lymphatic vessel invasion, colloid histology, or the penetration of tumour into or through the bowel wall) and can be adequately treated with a variety of local therapies.

##### *The role of mucosectomy alone*

With a moderate consensus it was agreed that early carcinomas limited to T1sm1, with well/good differentiated tumours, no evidence of blood or lymphatic vessel invasion and negative margins, can be safely and effectively resected by endoscopic mucosal resection (EMR) [46]. However, there is not enough evidence to recommend this procedure as the standard treatment. After EMR, pathologic analysis of submucosa infiltration is essential to assess the completeness of the resection [46].

##### *The role of local excision alone*

Patients with T1 small, exophytic, mobile tumours without adverse pathologic factors (i.e., high grade, blood or lymphatic vessel invasion, sm3) can be adequately treated with local excision alone, preferably a TEM procedure [47,48].

With a minimum consensus it was agreed that technically, the use of local excision requires that there is a non-obstructing tumour and its dimension is less than half of the lumen and/or size is less than 4 cm of diameter [48].

The specimen after local excision has to be carefully analyzed to evaluate its integrity, the depth of invasion in the bowel wall, the absence of margin infiltration both laterally and deeply, and the presence of adverse pathologic factors: high grade, blood or lymphatic vessel invasion.

When the muscular layer is involved by the tumour (T2), the risk of positive lymphatic nodes ranges between 15% and 20%. Local excision alone is an inappropriate procedure. It should only be

integrated with combined treatment (radiotherapy + chemotherapy), preferably preoperatively, when major surgery is contraindicated or refused.

In early localized tumours Transanal Endoscopy Microsurgery (TEM) may emerge as a technically reliable option to remove the full thickness of rectal wall and to evaluate the completeness of the removed specimen [47,48].

Local excision is associated with less anorectal and genitourinary dysfunction and better quality of life compared with radical surgery.

Local excision is not indicated in patients with cT3 tumour due to the usually large dimension of the primary lesion and the high incidence of positive nodes (30–50%).

At least half of the patients who undergo salvage abdominoperineal resection (APR) for local recurrence after local excision and/or radiotherapy can be cured: however, if these patients had been offered definitive surgery as the first treatment, cure rates would be higher.

##### *The role of standard resection*

cT2 rectal cancers and cT1 with high risk factors are adequately treated with standard resection with TME alone providing the nodes are negative (N0).

A standard resection done a few weeks after a local excision, when high risk predictive factors are present in operative specimen, does not compromise the oncological results compared to a standard resection done as the initial treatment in patients. However, depending on the tumour location, this may compromise the ability to perform a sphincter-sparing operation.

## **Intermediate stage (stages II–III resectable)**

Intermediate tumours are defined as neoplasms extending beyond the rectal wall but without unresectable infiltration to surrounding organs (c/p T3–4 or N1–2 M0).

##### *The role of TME*

Total Mesorectal Excision (TME) has changed dramatically loco-regional tumour control in rectal cancer surgery.

Local relapses after TME alone for pT3–4 N1–2 of the medium- or low-rectal cancer still range between 15% and 21% in randomized trials [35,49].

The efficacy of TME is closely related to the training and the volume of cases per year of each surgeon. The surgeon represents one of the major prognostic factors for the treatment of rectal cancer [50].

Population-based registries show that improvements in outcome after TME occur mainly in younger patients. Furthermore, 6-month postoperative mortality is significantly increased in elderly patients (> or =75 years of age) compared with younger patients (<75 years of age). For elderly patients who have good physical and mental status, the same treatment that is given to younger patients is appropriate. In contrast, for those with diminished physiological reserves and co-morbid conditions, alternative treatments that keep surgical trauma to a minimum and optimise the use of radiotherapy might be more suitable [51,52].

With a minimum consensus it was agreed that, by using anterior resection with TME radical surgery can be achieved also in distal rectal cancer since rectal cancer rarely grows more than a few millimetres distally from the macroscopic margin in the bowel wall, indicating that a distal margin of 1 cm will probably be sufficient for local cure in terms of intramural spread. If such an approach is considered, frozen section (during surgical intervention) is mandatory.

In patients with tumours in the middle or distal third of the rectum, lymph nodes or other tumour deposits can be found in the mesorectum up to 4 cm distally from the tumour. Complete removal of mesorectum distally is always indicated in these tumour locations [40,53].

In tumours located in the upper rectum a Partial Mesorectal Excision (PME) extending 5 cm below lower tumour margin and sparing the distal part of the mesorectum is feasible. However, definitive evidence for this is not available.

#### The APR planes

Pathological studies of the CRM at the level of the anorectal junction and anal sphincters show high risk of tumour involvement [54].

The quality of surgery in the levator/anal canal area below the mesorectum varies between surgeons who may operate in different surgical planes: intrasphincteric/submucosal plane, sphincteric plane and levator plane [1,55,56].

With an APR there are two planes: one for the mesorectum and one for the anal canal. It is crucial to have the correct strategy when an APR is performed. The dissection from above has to be stopped before entering the levator plane. The next step is to dissect from below outside the sphincteric plane and by doing so finally divide the levators from below. With this technique a waist in the specimen, or an “apple core” just at the place of the tumour, can be avoided and can prevent the specimen from having positive CRM [40,56–58].

#### The value of sphincter/organ-saving surgery

Sphincter preservation is usually considered when tumour is located in the lower third of the rectum. Since the mesorectum decreases in size close to the top of the anal canal, tumours arising in this area can easily invade surrounding structures, such as the levator muscles or the internal and external sphincters. Consequently, it is crucial to ensure that the pelvic floor is free from tumour if a loco-regional curative procedure, with the sphincters intact, is to be performed in very low T2 or greater rectal cancers [59].

From both single-institution series, randomized trials, and national registers the number of patients with preserved sphincters has increased from 25% up to 50–75% in the past 30 years. Moreover, there are centers of excellence, where the number of patients with preserved sphincters is as high as 90%, although it is always difficult to interpret these data due to selection bias and case mix. Based upon prospective population-based registration the proportion of patients in the total population having a sphincter-preserving procedure is approximately 65%.

Modern neoadjuvant radiotherapy in a setting has further changed surgical philosophy, since many surgeons claim that more sphincters can be preserved, provided that preoperative chemoradiotherapy is used [59].

Unfortunately, the randomized trials nor meta-analyses of the trials support this idea although a subgroup analysis of one of the large trials reported increased sphincter preservation [59]. When comparing recent data with historical controls, one has to take into account the main changes in rectal cancer surgery during the past 10–15 years. It seems that the change in surgical attitude may be more important than the effects of any preceding radio(chemo)therapy. As the Swedish Council of Technology Assessment in Health Care (SBU) pointed out, at this moment the literature is inconclusive in evaluating the role of preoperative radiotherapy alone or with concurrent chemotherapy in promoting sphincter-saving surgery in low-lying tumours [60,61].

Sphincter preservation without good function is of questionable benefit. Based upon reports, most patients are considered to have an acceptable to good function but as many as 20% will be more or less incontinent, not only for flatus or loose stool but also for solid stool. For some elderly and immobile patients a stoma can even be preferable to a preserved but moderately functioning sphincter. Based upon questionnaire studies stoma patients, as a group, do not have a worse quality of life than patients treated with sphincter preservation.

Cultural differences are significant. For example a stoma may be more or less disastrous for the patient than a local failure in southern parts of Europe and the Arabic world. Therefore, many patients from the Mediterranean areas will accept poor bowel function in preference to a stoma, and will also accept using diapers [59].

#### T4 unresectable rectal cancer

Locally advanced tumours are defined as neoplasms extending beyond the rectal wall with unresectable infiltration to surrounding organs or structures, and/or perforation of the visceral peritoneum (c/p T4 N0–2 M0).

#### The role of extended surgery

A rectal cancer is defined as unresectable if a potentially curative surgical resection is not feasible. The evaluation of resectability depends on the extent of the operation the surgeon is able to perform as well as the degree of morbidity the patient is willing to accept.

The heterogeneity of the presentation and a definition of resectability based on clinical criteria rather than on objective criteria make it difficult to compare between series [62].

It is important for the surgeon to recognize preoperatively the extent of tumour invasion into other organs and/or the pelvic sidewall for documentation prior to preoperative radiation and to establish a plan for *en bloc* resection [63].

From the surgical point of view, R0 resection represents the most important parameter to achieve the best long-term outcome in T4 rectal cancer in terms of overall survival, DF-SVV and local control.

After total pelvic exenteration, the morbidity rate is higher than 50% and includes: pelvic abscess or fistulas, sepsis, leak of the perineal suture, anastomotic leak, perineal wound infection, intestinal obstruction and pulmonary disease. Physiological age and the absence of co-morbidities appear to be more acceptable when selecting patients for exenteration than chronological age [64].

When partial resection of involved organs enables removal of all tumour (*en bloc* resection), a limited resection (without total pelvic exenteration) could be performed [63].

With a minimum consensus it was agreed that when the trigone of bladder or the prostate is involved, Total Pelvic Exenteration is recommended for all patients, irrespective of the response to preoperative treatment. This involves the removal of the rectum, bladder, lower ureters, internal genital organs and bilateral internal iliac vessels *en bloc* to achieve a negative margin and complete clearance of lymphatics [63].

A R0 total pelvic exenteration is a potentially curative operation for patients with advanced pelvic cancer: 5-year overall survival is acceptable (52–60%) [64], but it results in high morbidity and impaired quality of life.

Even if radical resection includes an extended lymphadenectomy with high ligation of the inferior mesenteric artery and lateral nodes dissection, the role of lateral lymphadenectomy has yet to be determined. Surgery extended to lateral pelvic nodes is associated with significant morbidity [63,65–67].

## Radiotherapy and chemotherapy

During the past decades different treatment modalities have been examined such as postoperative chemoradiotherapy with different 5-fluorouracil (5-FU)-based schedules, preoperative radiotherapy short course (5 × 5 Gy in 5 days) and long course (alone or in combination with 5-FU-based regimens or with new drugs), and intraoperative radiotherapy (IORT). These modalities are used differently in different parts of Europe and in North America, based upon the same evidence from studies performed in different parts of the world.

The evidence in the literature on the main advantages that a particular approach promoted for the different presentations of rectal cancer will be analyzed for early presentation of locally advanced and unresectable rectal cancers.

### Early localized tumours

Patients who have received standard surgery for an early, localized tumour do not need further therapy.

When patients with early, localized tumour have undergone a local surgical procedure, they are at risk for disease recurrence in the rectal wall or in the local nodes. Patients with pT1 tumours without adverse pathologic factors have a low rate of local failure (5–10%) and positive nodes (<10%) and usually do not need adjuvant therapy. On the contrary, when adverse pathologic factors are present or the tumour invades into or through the muscularis propria (pT2–3), the local failure rate increases to at least 17% and the incidence of positive nodes to above 10% and adjuvant treatments are recommended [68].

### The role of postoperative radio(chemo)therapy

With a moderate consensus it was agreed that the main advantage of surgery prior to irradiation is that pathologic details such as margins, depth of bowel wall penetration, and histological features are known.

Patients with pT1 tumours (after local excision) without adverse pathologic factors (involved margins, poorly differentiated tumour, sm3 and lymphovascular invasion) have such a low risk of loco-regional recurrence that adjuvant therapy is not recommended. However, there is a lack of evidence to demonstrate equivalent outcomes to radical surgery [69].

Patients with pT1 tumours (after local excision) with adverse pathologic factors (involved margins, poorly differentiated tumour, sm3 and lymphovascular invasion) or with any doubt about quality of the local excision procedure have to undergo a resection of the entire rectum. Postoperative radio(chemo)therapy could be considered for compromised general conditions or if the patient refuses surgery [69,70].

The optimal treatment of a pT2 tumour after a local excision is not clear, since large randomized trials are not available. Local excision alone is insufficient and radical surgery is therefore recommended. Postoperative radio(chemo)therapy is a reasonable alternative when adverse prognostic factors (involved margins, poorly differentiated tumour and lymphovascular invasion) are absent and the patient has co-morbidity or refuses surgery. However, in series with long-term follow-up, the pelvic failure rates are 18–25% [71].

Salvage of local failures is possible after local excision. In half of the patients, with local failure after local excision ± radio(chemo)therapy, local control can be achieved with salvage abdominoperineal resection (APR). Close follow-up to detect early relapse and then perform curative resection is recommended. Local recurrence after local excision and radiotherapy tends to occur late. In one series the median time from treatment to local recurrence was 55 months (range 26–91).

The series that have measured sphincter function after local excision and radiotherapy report favourable outcomes [71].

### The role of radiotherapy alone

External radiotherapy alone in early rectal cancer might be a feasible alternative to local excision in patients with poor medical condition or in patients who refuse any surgical treatment. However the evidence is limited and definitive recommendation requires further studies.

Contact therapy alone in early rectal cancer may be a feasible alternative to local excision, namely in patients with very poor medical condition and without adverse prognostic factors, or in patients who refuse any surgical treatment. However, this should be done in specialized centers and the number of available studies is limited [72].

### The role of preoperative radio(chemo)therapy

Preoperative short-course radiotherapy in clinically operable cT2N0 rectal cancers <15 cm from anal verge results in an even lower risk of local failure, but is usually not indicated since the absolute risk of a local failure in these early tumours is very low, provided very high quality staging and surgery can be performed. Recommendation for its use depends on interdisciplinary decision making and institutional preferences [35,49].

With a moderate consensus it was agreed that patients, who are either medically inoperable or who refuse radical surgery, can receive preoperative radiation followed by local excision. It is delivered usually with 5-FU-based concomitant chemotherapy, but a patient not fit for prolonged radio(chemo)therapy can receive short-course radiotherapy alone and delayed surgery. This approach is reported in only a few series and its use must be limited to only this subset of patients [48,73].

### Intermediate stage (stages II–III resectable)

There are two conventional treatment approaches for patients with intermediate-stage resectable rectal cancer. The first approach is preoperative radio(chemo)therapy followed by surgery if the tumour is uT3–4 and/or N+, and then postoperative chemotherapy can be considered. The second is initial surgery followed by postoperative combined modality therapy if the tumour is pT3 and/or N1–2 [1].

Four meta-analyses report partly conflicting results [74–76]. All of them reveal a decrease in local recurrence rates. The analysis by Camma et al. [74] and the Collaborative Colorectal Cancer Group [75] reported a survival advantage, whereas the analysis by Munro and Bentley [76] did not. The Swedish Council of Technology Assessment in Health Care (SBU) performed a systematic review of radiation therapy trials [77] and reported that survival is improved by about 10% using preoperative radiotherapy.

### The role of short-course preoperative radiotherapy

With a moderate consensus it was agreed that short-course radiotherapy definitively reduces local recurrence risk for patients with most rectal cancers. The relative risk reduction may actually be higher the lower the absolute risk of a local failure is. The largest absolute gains in the trials have been seen in patients with extramural spread and node-positive disease [35,49].

For patients with positive CRM, there is a reduction in local failure rates after short-course radiation. This is also seen in these locally advanced cases, although the magnitude of benefit is not sufficient [49].

After standardization of TME there is no evidence of overall survival benefit in the single short-course randomized trial [49]. The reduction in local failure rates in most intermediate cancers after TME standardization is too small to translate into an overall

survival benefit irrespective of which radiotherapy modality is used. However population-based studies have demonstrated that since standardization of rectal cancer surgery with TME and the implementation of preoperative radiotherapy there has been a survival benefit [35,45,49].

#### *The role of long-course preoperative radiotherapy*

The analysis of the randomized trials which compare preoperative radiotherapy with surgery alone showed that the combined treatment at biologically effective doses above 30 Gy decreases the relative risk of local failure. However, these analyses did not include only patients receiving long-course RT and most of the patients in the trials received short-course RT [74–77].

Since the standardization of TME there has been no randomized trial comparing long-course preoperative radiotherapy with surgery alone [74–77].

#### *The role of long-course preoperative radiochemotherapy*

Two recent randomized trials have showed an improvement in the results of preoperative radiation in patients with locally advanced rectal cancer when 5-FU-based chemotherapy is added to radiotherapy. A significant decrease in local recurrence was observed in those receiving chemotherapy as well as an increased rate of pCR. Five-year overall survival was not changed by chemotherapy, but the trials were underpowered to detect a 5% difference in overall survival [78,79].

After standardization of TME, there has been no randomized trial comparing long-course preoperative radiochemotherapy with surgery alone.

After preoperative radiochemotherapy a variable percentage of pathological complete response (pCR) specimens has been reported. Although some series show no correlation [80], many series report that patients who achieve a pCR following preoperative radiochemotherapy have improved long-term outcomes in terms of excellent local control rates and this is independent of their initial clinical T and N stages [81,82]. The increased incidence of pCR in the radiochemotherapy arms did not improve the final outcome of the randomized studies [78,83].

To increase the efficacy of bolus or infused 5-FU or capecitabine these agents have been combined, in several phase II studies, with oxaliplatin or irinotecan plus radiation. The apparently positive results of these studies have supported many ongoing phase III studies. At the present, infused 5-FU and oral fluoropyrimidines remain the standard agents to combine with preoperative radiotherapy [1].

About 20% of cT3N0 patients are overstaged and have cT1 or 2N0 disease and therefore are overtreated with preoperative radiochemotherapy. However, an even larger number would be understaged since following preoperative radiochemotherapy, 22% will have ypN+ disease. These data illustrate the weakness of nodal staging by imaging [84].

#### *Sphincter-saving after preoperative radio(chemo)therapy*

Sphincter preservation is usually considered when tumour is found in the lower third of the rectum. Since the mesorectum decreases in size close to the top of the anal canal, tumours arising in this area can easily invade surrounding structures, such as the internal and external sphincters and the levator muscles. This is common if the depth of invasion is beyond T2. Consequently, it is crucial to ensure that the pelvic floor is free from tumour if a loco-regional curative procedure, with the sphincters intact, is to be performed in very low-rectal cancer.

A non-significant improvement in sphincter-saving surgery was reported in a French study which randomized patients to surgery within 2 weeks after completion of radiation therapy, compared with 6–8 weeks. The long interval between preoperative irradiation

and surgery provided increased tumour downstaging with no detrimental effect on toxicity, but did not result in significant differences in long-term local control or survival [85].

#### *The role of adjuvant postoperative chemotherapy after preoperative radio(chemo)therapy*

There is insufficient evidence on the benefit of adjuvant postoperative chemotherapy after preoperative chemoradiation to come to a consensus about its use [1].

Exploratory post hoc subgroup analyses suggest that only patients who respond and are downstaged from cT3–4 to ypT0–2 benefit from 5-FU-based adjuvant chemotherapy [86]. These data supports that - as shown in other trials such as the > 800 patient QUASAR trial or the Japanese trial investigating 5-FU/FA or UFT, respectively, a significant survival benefit of 3–4% with 5-FU-based chemotherapy. The role of adjuvant treatment strategy after preoperative chemoradiation is still being investigated [87].

Both bolus and continuous infusion 5-FU as well as capecitabine have been combined in several phase II studies with oxaliplatin or irinotecan plus preoperative radiation as well as have been delivered alone as adjuvant treatment after surgery. However, the compliance of adjuvant 5-FU/LV in the adjuvant setting in the two large randomized phase II trials was suboptimal [78,79]. Ongoing phase III studies will help clarify the role of the combination of these new drugs.

#### *The role of postoperative radio(chemo)therapy*

The main advantage of postoperative radio(chemo)therapy is better selection of patients since it can be based on pathologic staging. Postoperative therapy was a common approach in North America, however since 2004 this is no longer the case. The primary disadvantages include an increased toxicity related to the amount of small bowel in the radiation field, a potentially more radio-resistant hypoxic post-surgical bed and, if the patient has undergone an APR, the radiation field has to be extended to include the perineal scar.

Four randomized trials have reported data on the use of adjuvant postoperative radiation therapy alone in stages pT3 and/or N1–2 rectal cancer [77]. No single study showed an improvement in overall survival as well as in the meta-analysis reports [74–76]. No survival advantage was observed from pelvic radiation plus elective para-aortic and liver radiation vs pelvic radiation alone [88].

In 1990, the NCI Consensus Conference, analyzing the postoperative North American chemoradiotherapy studies, stated that combined modality therapy was the standard postoperative treatment for patients with pT3 and/or N1–2 disease [89]. However, based on the German trial [90], most patients receive preoperative chemoradiotherapy in the US.

Although the 1990 NCI Consensus Conference recommended postoperative combined modality therapy for patients with pT3 and/or N1–2 disease [89], retrospective data suggest that there may be a subset of patients with pT3N0 disease who may not require adjuvant therapy. Reports from the MGH and Memorial Sloan Kettering, as well as data from a USA pooled analysis have identified favourable subsets of patients with pT3N0 disease who, following surgery alone, have a 10-year actuarial local recurrence rate <10% [91].

Their data suggest that patients with upper rectal cancers who undergo a Total Mesorectal Excision, have at least 12 nodes examined and have stage pT3N0 disease with an adequate radial resection margin likely do not need radiation therapy. The 4–5% benefit in local control with radiation may not be worth the risks.

With a moderate consensus it was agreed that a randomized trial suggested that radiation should start during cycle 1 rather than during cycle 3 [92]. However, more data are needed before recommending a change in sequence.

To address the associated toxicity, the contribution of adjuvant chemotherapy in the postoperative combined treatment has been questioned. Two European randomized trials support the argument. In a Hellenic trial [93] the chemoradiation alone arm was less toxic than the arm with 4 additional cycles of chemotherapy while maintaining the same efficacy. In a small Norwegian trial [94] chemoradiation had better survival than surgery alone. However, more data are needed before recommending a change in sequence.

#### *Pre- vs postradio(chemo)therapy*

Preoperative and postoperative therapies have been compared in randomized trials [35,90,95]. Two (Intergroup 0147 and NSABP R-03) closed early due to lack of accrual. The completed trial, the German Rectal Cancer Trial showed fewer local recurrences and less acute and late toxicity, but no survival benefit with preoperative therapy. In one trial when short-course preoperative radiation was compared with long-course RT alone and in another trial when it was compared with long-course chemoradiation for the subsets with a high risk of recurrence, more favourable results were seen in the preoperative arms.

At the present time, given the improved local control, and acute and long-term toxicity profile, reported in the German trial, patients with cT3 rectal cancer who require additional therapy to surgery (chemoradiation or short-course radiotherapy) should receive it preoperatively [35,83,90].

In two randomized trials preoperative short-course RT was compared with postoperative radiotherapy alone or with chemoradiotherapy in patient with CRM+ [35]. Preoperative short-course RT resulted in better local control than postoperative RT or chemoradiation, and in the latter trial also in disease-free survival [35,95].

#### *T4 unresectable*

##### *The role of long-course preoperative radio(chemo)therapy*

All patients with primarily unresectable disease should receive preoperative chemoradiation. This includes radiation in the range of 50–54 Gy plus 5-FU-based chemotherapy with the goal of increasing R0 resectability [77,96].

Given the limitation of the total radiotherapy dose which can be delivered to the bulky tumour in the pelvis and the frequent problem of local recurrence, the surgeon should be aggressive and not risk leaving microscopic residual tumour. Extended surgery to the infiltrated organs should still be considered even if there is a favourable response after preoperative therapy [97].

An alternative strategy under clinical evaluation for patients who are not medically able to receive long-course chemoradiation is short-course RT followed by delayed surgery [73].

##### *The role of radiotherapy intensification (altered fractionation, IORT)*

Although 50–90% of patients will be able to undergo a resection with negative margins, depending on the degree of tumour fixation, many still develop a local recurrence. To reduce this concomitant or sequential boosts can be delivered in preoperative setting with the goal of increasing the dose. However, doses above 50.4 Gy may be associated with a higher complication rate. Positive evidence of the role of higher dose is still to be confirmed in randomized studies [98–101].

To increase local control of unresectable rectal cancer a large single dose (10–20 Gy) of radiation by electron beam or brachytherapy (Intraoperative radiation or IORT) can be delivered to the tumour bed. Most North American and European single-institution studies suggest a favourable local control rate in patients who also have positive margins or microscopic residual disease [102,103]. However, not all series show a benefit [104].

The results (and recommended dose) of IORT depend on whether the margins of resection are negative or whether there is microscopic or gross residual disease. IORT does not compensate a suboptimal surgery. In general, series have used 10–20 Gy. IORT-related toxicity increases with IORT doses >18–20 Gy.

#### *The role of adjuvant chemotherapy*

The high incidence of metastases in unresectable patients is the rationale for the use of adjuvant chemotherapy after chemoradiation and surgery. However the definitive study in this subset of patients is not available [96].

#### *M1 (single or Oligo Met)*

Approximately 2–5% of rectal cancers are diagnosed with one synchronous metastasis or a few synchronous metastases in one organ, usually liver. These patients are staged as having oligometastatic disease, and can be treated in a potentially curative fashion.

#### *The role of chemotherapy*

With a moderate consensus it was agreed that combinations of drugs have shown promising activity in the group of patients with potentially resectable oligometastatic disease plus radical liver surgery. Chemotherapy can be delivered as initial therapy in patients with oligometastatic disease. However, the definitive study in this subgroup of patients is not available [105].

#### *The role of surgery*

With a moderate consensus it was agreed that surgery of synchronous metastasis limited to one lobe of the liver and/or of the lung, as well of the primary, is recommended.

The limited evidence does not identify the best timing for the surgery for the primary: either concomitant with resection of the metastases or delayed until after (chemo)radiation. It should be based on the individual patient.

#### *The role of pelvic radiotherapy*

The limited evidence does not identify the best timing for radiotherapy of the primary. Options include initial 5-FU-based chemoradiation, chemotherapy followed by chemoradiation and surgery of metastases, or initial short-course radiotherapy followed by chemotherapy and delayed surgery or chemotherapy followed by short-course radiotherapy and immediate or delayed surgery [73]. Patients who respond to chemotherapy should be treated if they are at risk of pelvic failure and/or progression.

### **Treatment toxicity and quality of life**

#### *Sphincter/stoma*

With a moderate consensus, in patients who have very low anastomoses, the colonic J-pouch (CJP) is superior to the straight colo-anal anastomosis when measuring bowel function. Side-to-side anastomosis has similar bowel function outcome compared with CJP. There is no agreement regarding the benefit of coloplasty [106].

With a moderate consensus it was agreed that in cases where the sphincter cannot be saved a permanent colostomy is the best option [107]. Total anorectal reconstruction (TAR) is an experimental option for patients who refuse a stoma.

With a moderate consensus it was agreed that impairment of sphincter function may be due to damage to autonomic nerves by surgery or radiotherapy or both. Excluding the sphincter from the irradiated volume can diminish the negative influence on sphincter function. All radiotherapy modalities (preoperative, post-

operative, either short or long course) seem to have the same detrimental effect [108–110].

With a moderate consensus it was agreed that a common technique used today to make stoma care more convenient for selected patient is to use a retrograde irrigation system, where patients empty the bowel every second or third day using an enema. By doing so only a pad is needed to cover the stoma instead of a stoma bag.

#### Bowel

There is strong evidence from the literature that bowel function will be adversely affected by both preoperative [107,108] and postoperative irradiation [111].

During chemoradiation, acute side effects such as diarrhea and increased bowel frequency (small bowel), acute proctitis (large bowel), and dysuria are common. These are usually transient and resolve within a few weeks following the completion of radiation.

With a moderate consensus it was agreed that with the conventional radiation dose range, the acute symptoms appear to be a function of the irradiated volume and the fraction size. Positioning devices (i.e., bellyboard) can be used to reduce small bowel toxicity. Dietary counseling is useful in the management of diarrhea. Bladder distension appears less reproducible in reducing the volume of small volume irradiation.

The use of concurrent chemotherapy, e.g. 5-FU which in itself may have significant GI toxicity, will exacerbate the acute GI effects of radiation [78]. The most common delayed severe complications are due to small bowel damage and include small bowel enteritis, adhesions, and small bowel obstruction requiring surgical intervention. The long-term bowel function is impaired more by postoperative radiotherapy than by preoperative radiotherapy [90].

The incidence of small bowel obstruction requiring surgery following postoperative pelvic radiation for rectal cancer is 4–15% in historical series [90].

In one randomized trial, the incidence of long-term toxicity is similar for preoperative short-course preoperative radiotherapy and long-course 5-FU-based chemoradiation [83].

#### Genitourinary

Urogenital dysfunction after rectal cancer treatment is common. Surgical damage to the pelvic autonomic nerves is the main course of urinary dysfunction. The incidence of new urinary incontinence after TME alone approaches 34% in one report. The influence of radiotherapy on the urinary function remains controversial [112].

#### Sexual habit

As with surgery, radiotherapy can lead to increased sexual dysfunction. In males a long-term deterioration of ejaculatory and erectile function is due to late radiation damage to the seminal vesicles and small vessels, respectively. In females, radiotherapy leads to vaginal dryness and diminished sexual satisfaction [107].

Surgical damage to pelvic autonomic nerves might be involved. During presacral mesorectal dissection damage to the superior hypogastric plexus and hypogastric nerves can occur, resulting in urinary incontinence, ejaculatory dysfunction in male patients and reduced lubrication in female patients. During dissection of the lateral planes of the mesorectum deep in the pelvis the sacral splanchnic nerves and the inferior hypogastric plexus are at risk, leading to urinary retention, erectile disorders in male patients and reduced labial and vaginal swelling in female patients [113].

Patients who undergo an APR have more voiding difficulties, erectile dysfunction and dyspareunia, compared with those who undergo a LAR [107]. This can be explained by the fact that more nerve damage occurs after an APR, especially during the perineal phase, during which the distal branches of the pelvic autonomic nerves are at risk. Because exact nerve identification can be difficult, the use of a nerve stimulating device could possibly facilitate preservation of the pelvic autonomic nerves during TME.

#### Follow-up

The main aim of clinical follow-up is to improve survival. This is achieved in two ways, by detecting recurrence of primary disease and/or by detecting a metachronous tumour. Other goals of the follow-up are: management of the posttreatment late complications, improvement of the patient–doctor relationship and documenting the quality of the therapy outcome.

#### Design and cost-effectiveness

##### General approach

The value of following patients after radical resection for colorectal cancer is still controversial, and scientific evidence supporting it remains sparse. Many cohort and case-control studies have supported the effectiveness of follow-up [114] but, very few randomized controlled trials have been performed correlating follow-up and cancer mortality.

Moreover, the frequency of follow-up is still debatable. Outcome of follow-up programs can be considered from both efficacy and cost perspectives. Despite limited evidence, follow-up programs are being used in most clinics and these support a continued relationship with the patients. An annual CT for high risk patients seems to be justified [115,116].

Two systematic reviews with meta-analyses were published the same year investigating the same five randomized controlled trials [115,117], with the same conclusion: more intensive follow-up decreases mortality in colorectal cancer compared with sporadic or less intensive follow-up. Subsequently, another randomized study not included in the meta-analyses was published and it confirmed this conclusion.

The quality of surgery in these trials has also been questioned, as very high local recurrence rates were seen in the two studies which showed most benefit from intensive follow-up.

The published studies imply that finding extraluminal recurrences (local recurrence after rectal cancer and liver metastases after colorectal cancer) is the main benefit in the follow-up program. Since local recurrence after colorectal cancer surgery is much less common than historical data, the principal benefit remains detecting liver and possibly lung metastases, allowing the opportunity for a second curative procedure.

Despite this the Current Oncological Practice is moving towards high intensity follow-up programs. A minimum acceptable practice should be based on the diagnostic tools available in each country.

The search and identification of an intraluminal recurrence does not change mortality, however, the detection of metachronous colorectal malignancy may be worthwhile. The calculated annual incidence is 0.35% for the identification of metachronous lesions, with accumulative incidence at 18 years of 6.3%.

Long-term analyses of the Uppsala and Swedish Trials show an increased risk of second cancers in patients treated with RT in addition to surgery for a rectal cancer. This was mainly explained by an increase in the risk of second cancers in organs within or adjacent to the irradiated volume. However, an overall favourable effect of radiation still dominates, as shown by the reduced risk of local recurrences compared with the increase in second cancers [118].

### Early localized tumours

In patients who undergo traditional surgery (anterior resection or APRn with TME) for early rectal cancer, the risk of local and distant recurrence is very low. A colonoscopy is recommended at 3 years and then, if normal, once every 5 years thereafter, to rule out a metachronous colorectal cancer [116,119,120].

After local excision, follow-up should include regular endoscopic surveillance of the rectum, especially the scar. Careful follow-up to diagnose local recurrence early is necessary so that salvage surgery can be performed [121].

With a moderate consensus it was agreed that a protocol similar to that followed for rectal cancers treated with conventional surgery may be employed after local excision, although with more frequent assessment over a longer period to early detect local recurrence.

The use of modern imaging (endorectal ultrasonography, MRI and PET) to detect local recurrence is recommended after local excision, but the appropriate frequency is subject of debate and firm data are pending [121].

Digital rectal examination and sigmoidoscopy are recommended, after local excision, every 3 months for the first 3 years, every 6 months for the next 2 years and then annually. However, the acceptable frequency is not unanimously agreed upon.

### Intermediate and locally advanced tumours

**History and physical examination:** There are no data that directly address the contribution of the history and physical examination to outcomes of colorectal cancer surveillance. A clinical history and pertinent physical examination should be performed every 3–6 months for the first 3 years and annually thereafter [119].

**Carcinoembryonic antigen (CEA):** Even if 30% of all colorectal cancer recurrences do not produce CEA, elevated CEA levels, if confirmed by retesting, warrant further evaluation for metastatic disease but do not justify the institution of systemic therapy for presumed metastatic disease [119].

**Complete blood cell count (CBC):** Currently there is no evidence to suggest the use of CBC in routine follow-up after colorectal cancer resection [119].

**Liver function tests (LFTs):** No studies have shown the usefulness of LFTs in the monitoring of patients after colorectal cancer resection. Because of low specificity, routine use of LFTs in surveillance of colorectal cancer is not recommended [119].

**Colonoscopy and flexible proctosigmoidoscopy:** A second or synchronous malignancy at a different location within the colon or rectum is found in 3–7% of patients who have undergone resection. Another 25% of these patients will have adenomas that require removal.

All patients should have a colonoscopy for the pre- or perioperative documentation of a cancer- and polyp-free colon. The data are sufficient to recommend colonoscopy every 3–5 years to detect new cancers and polyps. Routine annual colonoscopies are not recommended [119].

Numerous studies have attempted to document the usefulness of colonoscopy or flexible proctosigmoidoscopy in the detection of recurrent colorectal cancer. These studies have found that they were rarely the first indicator of recurrence (0–19%) [119].

With a moderate consensus it was agreed that chest X-rays have a low frequency of initially detecting pulmonary metastasis (range, 3–20%). Despite their low cost, the advantage in outcome is small. The current available data do not support routine chest X-ray in the follow-up evaluation of colorectal cancer [119]. Chest X-rays may be ordered to diagnose abnormalities prompted by elevated levels of CEA or for patients who have symptoms suggestive of pulmonary disease [119].

With a moderate consensus it was agreed that no studies have proven that the routine use of CT scan can identify curable metastatic disease before other imaging modalities. The use of periodic

CT scans in the postoperative setting is unproven. However, CT scanning is useful to evaluate suspicious signs and symptoms in patients such as increasing CEA level, abdominal pain, and abnormal LFTs. Further studies are needed to evaluate the role of routine CT scanning in patients with non-CEA producing tumours [119].

With a moderate consensus it was agreed that multidetector-row CT (MDCT) has a major role in the follow-up of rectal cancer patients, because it provides good imaging of the liver and the abdomen and chest in one session. Several studies have assessed the value of using thin slices to improve detection of small metastases. However its use has to be first properly evaluated and then based on the diagnostic tools available in each country.

MRI showed superior accuracy than conventional CT in the detection of rectal cancer recurrence by the combination of the signal intensity on T2 weighed images, the shape of the margins of the mass and the presence of greater than 40% contrast enhancement. Multidetector CT and FDG-PET-CT are similarly accurate in the definition of the presence of a local recurrence [122].

Ultrasound and chest X-ray are used as primary screening tools for the detection of transabdominal metastases. However, for the high risk group (stage III) both methods are insufficiently sensitive, and CT of the chest plus abdomen is preferred.

A meta-analysis compared the diagnostic value of US, CT, MRI and PET in the detection of gastrointestinal cancer metastases. FDG-PET with CT is the most sensitive method for detection of metastases, with a mean weighted sensitivity of 90–92% [123]. There is not sufficient evidence that routine use of FDG-PET is cost-effective.

The selection of patients for individualized follow-up, based on tumour stage and age of the patients, is recommended.

In patients who receive neoadjuvant therapy, recurrences after 5th year from surgery can occur [49,86]. Surveillance beyond the 5th year from diagnosis should be performed in patients submitted to preoperative therapies.

### Research scenario

In this time of changing therapeutic approaches, a common standard for large heterogeneous patient groups will likely be substituted by more individualized therapies. It will depend on new evidence of more tailored diagnosis, surgery, radiotherapy and chemotherapy. The main questions addressed by ongoing research in these different fields are outlined.

### Diagnostics

#### T substaging

Substaging of T3 tumours by MRI has been proposed to identify different risk groups. This is defined as the distance of tumour spread from the outermost edge of the tumour to the muscularis propria of the rectal wall. This has been validated prospectively by the MERCURY study group and it has shown direct agreement between the measurement of extramural depth of spread and corresponding pathology. Increasing depth of spread is associated with poor prognosis and T3a and T3b tumours (tumour spread <5 mm with safe circumferential resection margins) have a favourable prognosis compared with T3c and T3d tumours (T3c is >5 mm and <15 mm, T3d is >15 mm). Evidence from correlation with imaging and histopathology shows that this is the most accurate method of staging rectal cancer and allows accurate prognostication based on these measurements. This proposal is under clinical evaluation [124].

#### N staging

Identifying nodal disease is a diagnostic problem for the radiologist. Recent developments have shown that MRI with lymph

node-specific contrast enhancement may be the most promising modality for distinguishing between the lower risk N0 and higher risk N1 and N2 rectal cancer patients, but their role is still under clinical evaluation.

#### Diffusion MRI

Perfusion indices and apparent diffusion coefficients inside the tumour region seemed to be of predictive value for the outcome of preoperative therapy in patients with primary rectal carcinoma. MRI diffusion-weighted imaging (DWI) in combination with T(2)-weighted imaging (T(2)WI) for the detection of rectal cancer as compared with T(2)WI alone seems in preliminary reports to provide better identification of rectal cancer and local nodes. Ongoing research will clarify the role of this imaging modality.

With a moderate consensus it was agreed that in preliminary reports, diffusion-weighted MRI seems to be reliable to monitor the therapy response and to predict prognosis in patients with primary rectal carcinoma. However, further studies are needed.

#### FDG-PET-CT

FDG-PET with contrast enhanced CT protocols could become a single-step staging procedure in evaluating metastases at the diagnosis, but its role is still under clinical evaluation. At this time the evidence is limited

#### Surgery

##### Organ preservation

After preoperative chemoradiation a variable percentage of pathological complete response (pCR) specimens is reported. Although some series show no correlation, many series report that patients who achieve a pCR following preoperative chemoradiation have improved long-term outcomes in terms of excellent local control rates, independent of their initial clinical T and N stages, even if the different pCR rates in chemoradiation arms did not affect the final outcome in the randomized studies. These data support the concept of heterogeneity among rectal cancers and the need to identify reliable markers to detect favourable patients who could be cured with less surgical therapy.

Organ preservation represents one of the ongoing topics of surgical research: the experience with preoperative chemoradiation followed by local excision is being investigated. Most series are limited to highly selected patients with cT3 disease who either are medically inoperable or refuse radical surgery. Since most series limit this approach to those patients who responded to preoperative therapy there is a need to identify prognostic and predictive factors to better define patients who are suitable for limited surgery. Trials are ongoing.

It is questioned if a local excision can be avoided if the tumour has regressed completely following radiotherapy. Intensive follow-up with the “wait-and-watch” philosophy has been advocated by one group with impressive results, similar to those seen after radiotherapy for anal carcinoma [125,126]. This treatment policy has been adopted in patients where an APR has been the alternative procedure. However, it must be emphasized that this is an investigational approach and the standard of care remains surgery.

##### Laparoscopy surgery

Laparoscopic rectal cancer surgery seems to offer less blood loss, less pain, earlier return of bowel function and shorter hospitalization. The long-term impact on oncological endpoints awaits the findings from large ongoing randomized trials [127].

##### Cylindric APR

Pathological studies of the CRM at the level of the anorectal junction and anal canal show a high risk of tumour involvement.

A waist is often created by the surgeon where the mesorectum terminates and the levator (m. puborectalis) inserts into the sphincter complex. The quality of surgery in the levator/anal canal area below the mesorectum varies between surgeons who may operate in different surgical planes. Prospective studies on the reliability of the levator plane to reduce CRM+ are under clinical evaluation [40,44].

#### Radiotherapy and chemotherapy

##### RT schedule

There is a study underway which compares short-course vs long-course preoperative radiotherapy. Hopefully this study will create an opportunity for a more tailored approach based on stage, location of the tumour, and the prediction of the CRM.

Data from the Uppsala group have shown that short-course radiotherapy and delayed surgery in T4 tumours based upon MRI staging also result in a chance of R0 resection, indicating that downsizing will occur after this treatment regimen [73]. Ongoing studies are evaluating the role of short-course radiotherapy and delayed surgery in resectable patients.

##### RT + chemo

Open questions of intensification of preoperative chemoradiation and postoperative adjuvant treatment are currently addressed by three large trials (CAO/ARO/AIO-04 in Germany, PETACC 6 in Europe, and NSABP R-04 in the US). They investigate the value of oxaliplatin in addition to preoperative chemoradiation with 5-FU (CAO/ARO/AIO-04) or capecitabine (PETACC 6) as well as in the postoperative phase for the prolonged period of 4–5 months. The NSABP R-04 trial compares capecitabine with 5-FU in a 2 × 2 factorial design with or without oxaliplatin.

In patients treated with 5 × 5 Gy preoperatively, postoperative chemotherapy has not been evaluated so far but is currently being tested in a randomized trial (SCRIPT trial, “Simply Capecitabine in Rectal cancer after Irradiation Plus TME”).

An Italian trial (INTERACT-LEADER) is testing a combination of preoperative radiotherapy with capecitabine and oxaliplatin vs accelerated radiotherapy by concomitant boost and only capecitabine. The cT3N0–1 MRI responding patients receive local excision, and if pCR is confirmed no further surgery is performed.

The early delivery of highly active systemic combination treatment before chemoradiation and TME is currently being investigated in phase II trials. Both approaches indicate that treatment of advanced rectal cancer has become truly ‘multidisciplinary’, requiring improvement in all fields of surgery, radiation and chemotherapy for optimal local control and reduction of distant metastases in order to improve overall prognosis.

##### RT – chemo + target therapy

The next generation of clinical trials are beginning and will integrate novel ‘targeted’ drugs such as bevacizumab and cetuximab in both the preoperative and postoperative settings. The epidermal growth factor receptor (EGFR) is a promising target of antitumour treatment because it is involved in cell division, inhibition of apoptosis, and angiogenesis. Current trials with a traditional sequence/timing did not show improved results indicating that more intense preclinical investigations are needed to identify the relationship with metabolic constrains (K-ras) and to establish the best sequence of triple combinations [128,129].

Inhibition of vascular endothelial growth factor (VEGF) via an anti-VEGF antibody (bevacizumab) has been shown to block the growth of a number of human cancer cell lines, including colorectal, in nude mice. Preliminary clinical data indicate significant activity, however data on safety are limited [128]. Several trials are ongoing regarding this issue.

In the face of current and future schedules and the increasing number of therapeutic options and intensities, translational research is urgently required for the identification of patient groups, by both clinical-pathological features and molecular and genetic markers, that will gain maximum benefit from each treatment option.

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