Preoperative decision making for rectal cancer

Panagiotis Taflampas, M.D. a,*, Manousos Christodoulakis, M.D. b, Eelco de Bree, M.D. b, John Melissas, Ph.D. b, Dimitris D.A. Tsiftsis, Ph.D. b

aSecond Department of Surgery, Venizeleio Hospital, PO Box 44, 71409, Herakleion, Greece; bDepartment of Surgical Oncology, Medical School of Crete University Hospital, Herakleion, Greece

Abstract

BACKGROUND: Rectal cancer treatment has become multimodal as a result of significant advances in imaging, staging, surgery, radiotherapy, and chemotherapy. Multidisciplinary teams can incorporate these developments into tailor-made treatment plans and offer state-of-the-art services for rectal cancer patients.

METHODS: We searched the MEDLINE and PubMed databases using the following keywords: "rectal cancer," "total mesorectal excision," "multidisciplinary treatment/team," "radiotherapy," "chemotherapy," and their combinations. There were no language or publication year restrictions. References in published articles also were reviewed.

RESULTS: Total mesorectal excision surgery, high-resolution pelvic magnetic resonance imaging, preoperative chemoradiotherapy, and pathologic reports according to Quirke protocol are preconditions for the initiation of an effective multidisciplinary team. Common topics for discussion are the status of the circumferential margin, the type of radiotherapy and surgery required, and the chemotherapeutic agent to be used.

CONCLUSIONS: This review focuses on this issue based on two main principles. First, the status of the circumferential margin dictates the use of preoperative chemoradiotherapy. Second, preoperative chemoradiotherapy is superior in terms of free circumferential resection margin rate, local recurrence rate, and toxicity.

© 2010 Elsevier Inc. All rights reserved.

KEYWORDS: Rectal cancer; Multidisciplinary team; Radiotherapy; Cancer treatment; Multidisciplinary treatment; Total mesorectal excision

Carcinoma is defined as rectal when its distal margin is localized within 12 cm from the anal verge. This definition is arbitrary and is based on epidemiologic data showing significantly higher local recurrence (LR) rates between this subgroup and patients with colon cancer. During the 1990s, surgery and postoperative adjuvant chemoradiotherapy (CRT) reserved for locally advanced tumors was the gold standard treatment regimen. This worldwide approach had been derived from the principles of colon cancer treatment.

As previously mentioned, the LR rate of rectal cancer is markedly higher than that of colon cancer. This is attributed to anatomic restrictions (narrow bony pelvic field) and technical difficulties in obtaining clear resection margins. The high LR rates observed, despite the use of postoperative CRT, was the reason investigators decided to test preoperative radiotherapy (RT) or CRT. The rationale behind this shift was that because preoperative RT is applied to virgin, well-oxygenated tissues, the effect on LR rate and survival would be more profound compared with postoperative CRT. In addition, preoperative CRT could downstage the tumor and make radical resection feasible in most cases. Other advantages of preoperative RT are less small-bowel toxicity and the absence of a newly constructed anastomosis.
in the irradiated field. The results of preoperative RT and CRT were promising and established this alternative option in rectal cancer treatment. The pioneering work of Heald et al. showed that conventional surgical technique for rectal cancer (blunt pelvic dissection) had a significant impact on the LR rate and survival. On the basis of embryologic and anatomic studies, they proposed total mesorectal excision (TME) as an alternative option, in which sharp dissection is made under direct vision across specific embryologic avascular planes. TME was a major breakthrough in rectal cancer treatment because its use significantly reduced LR rate and increased survival. TME is now considered the gold standard for the surgical treatment of rectal cancer.

Computed tomography (CT) has been used traditionally for rectal cancer staging. Local evaluation focused on enlarged lymph nodes and infiltration of adjacent organs. The dominance of TME and the option of preoperative CRT raised new issues that CT could not address because of its low spatial resolution. Circumferential resection margin (CRM) is defined as the distance from the edge of the tumor to the margin of the resected specimen and has been proven to be a credible surrogate marker for LR rate. Although the tumor-node-metastasis (TNM) staging system does not yet incorporate CRM as a prognostic parameter, it has become a key issue for modern rectal cancer treatment. Recent studies have shown that pelvic magnetic resonance imaging (MRI) can predict the CRM status (free or involved) with relevant accuracy and MRI—despite its drawbacks—has gained its place in rectal cancer imaging. Pelvic MRI now is used widely for the preoperative treatment planning of rectal cancer.

The contribution of medical oncology to rectal cancer locoregional treatment had been restricted for a long time to adjuvant treatment (5-fluorouracil) combined with postoperative RT. Studies on preoperative RT showed that the addition of chemotherapy further reduced the LR rate and improved survival. Recently, novel agents such as oral fluoropyrimidines, irinotecan, and oxaliplatin have been added as credible options for preoperative CRT.

Pathologic reports of rectal cancer specimens classically have been concerned about lymph node status and tumor differentiation. TME surgery and pelvic MRI oriented pathology in a new pathway. CRM, as stated earlier, has been shown to correlate with LR and survival. State-of-the-art pathologic examination of the rectal specimen is a combination of macroscopic and microscopic features with emphasis on the CRM. Modern pathology classifies rectal cancer resection according to its quality and provides data for effective auditing.

These parallel and significant advances in different fields of medicine all targeted to improve results for rectal cancer patients offer several options for the preoperative management of rectal cancer. Similar to breast cancer, rectal cancer treatment requires careful preoperative planning concerning the use of available treatment modalities and their sequential use (surgery, RT, and chemotherapy). Rectal cancer treatment has become multidisciplinary in nature involving at least surgeons, radiologists, radiotherapists, pathologists, and medical oncologists. This interconnection should commence at the time of the initial diagnosis. The preoperative handling of rectal cancer patients affects LR and survival and very often postoperative therapy schemes cannot compensate for any mistakes during the initial decision making. A multidisciplinary team (MDT) can provide tailor-made treatment options for any given rectal cancer patient. Treatment out of the context of a MDT currently varies according to local dogma, facilities, and resources.

This review discusses current developments, focuses on the essential preconditions for the initiation of an MDT (Table 1), and proposes an algorithm for the management of locoregional rectal cancer based on preoperative pelvic MRI and CRT (Fig. 1).

**Preconditions for the formation of an effective MDT**

**TME**

The primary goal of rectal cancer surgery is to achieve a microscopically radical (R0) resection. In reality, LR may present the evolution of residual disease, which has gone unrecognized during surgery. Small fragments of local tumor that have been left in situ continue to grow to form the future focus of LR.

Variability in surgical technique affects survival and LR rate. Heald et al. proposed TME as the optimal surgical approach for rectal cancer surgery. TME is based on embryologic and anatomic examinations and achieves radical resection of the mesorectal envelope and subsequently all tumor deposits and positive lymph nodes along with the blood supply and lymphatic drainage along avascular planes without compromising bladder and sexual function. TME is based on the concept that cancer spread will stay confined within the embryologic mesorectal envelope at least during the early stages of the disease. Straying into the mesorectal envelope during rectal surgery is a major cause of residual disease and LR. Straying outward may damage the autonomic nerves and is a major factor for sexual and urinary disturbances. The results of the first series of 100 patients by Heald et al. were remarkable, reporting a 0% two-year LR rate without any postoperative adjuvant therapy. Despite the
lack of a prospective randomized study comparing TME with conventional rectal surgery, many centers from Europe and the United States reported LR rates of less than 10% using TME. These results compare favorably with historical controls in which the LR rate often was higher than 30% to 40%. The results of TME are so impressive that many countries, for example, Sweden and Norway, adopted live surgical and video training programs nationwide on TME. The implementation of these programs resulted in improved results nationwide. TME is the gold standard for the surgical treatment of rectal cancer involving the middle and lower third of the rectum. For the upper third of the rectum, TME is not considered obligatory (removal of the mesorectum to the level of the levator muscles), rather a more conservative resection called tumor-specific TME is preferred (removal of the mesorectum 5 cm distal of the tumor).

Proper education is essential to achieve optimal results. This may be accomplished by clinical fellowships dedicated to rectal cancer surgery. By adhering to TME details the surgeon collaborating in the MDT removes the surgical variable from the equation of rectal cancer treatment. Continuous surgical audit is necessary to maintain excellent surgical results and improve the primary and secondary end points during quality control of rectal cancer treatment.

**Pelvic MRI plus expert radiologist**

The main issue concerning local staging of rectal cancer is the status of the CRM. CT cannot delineate CRM accurately and currently is not used with this indication. The use of pelvic MRI is considered the first essential step toward a multidisciplinary approach to rectal cancer. MRI can predict the status of the CRM and whether the planned surgical resection is to be curative. MRI will classify patients into categories that are at varying risks of LR and in need of different approaches concerning their preoperative treatment strategy. In addition, fine-slice, high-resolution MRI can visualize the surgical planes for rectal cancer surgery preoperatively and provide a surgical roadmap for the surgeon, especially in technically demanding cases. Furthermore, MRI may visualize large T4 tumors invading pelvic structures and provide the surgeon and the patient with an alternative option, that is, referral to a specialized center for pelvic exenteration.

The high-resolution, thin-section pelvic MRI with phased-array body coils is the first step before treatment decisions are made. At least one radiologist with special interest and education in pelvic MRI interpretation must participate in the MDT to provide the necessary data derived from the MRI.

**Preoperative four-field radiotherapy**

The excellent results of TME challenged the beneficial effect of preoperative RT. Early studies showing benefit from the use of RT involved patients who had undergone conventional blunt dissection and not TME. A Dutch study, however, showed that preoperative RT reduced the LR rate also after standardized TME surgery. Sauer et al. in a landmark prospective study, compared preoperative versus postoperative CRT. A total of 823 patients were randomized to either preoperative or postoperative CRT (5,040 cGy plus 5-fluorouracil infusion). They concluded...
that preoperative CRT was superior in terms of LR rate (5-year LR rate, 6% vs 13%) but no survival benefit was observed. In addition, acute and long-term toxicity was significantly less in the preoperative arm. This randomized study showed the superiority of preoperative CRT for rectal cancer. Furthermore, the MRC CR07 (Medical Research Council funded CR07 trial) randomized trial showed that postoperative CRT for patients with involved CRM does not compensate for the beneficial effect of the routine use of the short scheme for all rectal cancer patients. The CRM status is the strongest predictive factor for LR after multivariate analysis. CRM is used widely as a surrogate marker for the LR rate and survival.

The availability of preoperative RT is a precondition for the initiation of a MDT. Furthermore, RT delivery through at least 4 fields is essential because factors such as total dosage, fragmentation, and the number of fields used are contributors to the efficacy and toxicity of CRT.

Pathology report

Quirke et al. proposed a detailed system for the macroscopic and microscopic examination of the rectal specimen. The assessment of the completeness of the mesorectal excision is essential and provides prognostic information for LR and survival. The distal margin should be at least 1 cm when measured in the fresh specimen. The integrity of the mesorectal fascia is examined and defects are recognized. Such defects are surrogate markers of residual mesorectal tissue that may harvest cancer cells that may give rise to LR. The quality of mesorectal excision can be characterized as optimal, suboptimal, or poor. Treatment plans consistently are audited for positive CRM rates, LR rates, and overall survival. The examination of the rectal specimen according to Quirke protocol is a precondition for the initiation of an MDT. The detailed and oriented examination of the rectal specimen is a precondition for the initiation of an MDT.

New chemotherapeutic agents

The addition of chemotherapy to RT offers complete remission rates that may be as high as 38%. In fact, complete pathologic remission is associated with increased survival after CRT for rectal cancer. In this context, new agents aiming at higher percentages of pathologic remission have been investigated. Oral fluoropyrimidines (ie, Xeloda, Roche, UK) show similar outcomes, in terms of local control and overall survival, with intravenous infusion whereas oral administration is very convenient for the patient. Irinotecan and oxaliplatin in combination with 5-fluorouracil have been used concomitantly with RT in the preoperative setting with promising downstaging (67%–84%) rates. Biological agents such as bevacizumab and cetuximab have been used in combination with other drugs during CRT and have proven to be safe.

The medical oncologist should suggest which drug regimen is appropriate for administration during CRT and evaluate the eligibility of a patient for participation in ongoing clinical trials.

Common topics in MDT meetings

Staging and CRM evaluation

According to TNM, the depth of the tumor (T1–4), lymph node infiltration (N0–3), and the presence of metastases (M0–1) are the basic predictors of survival and used to stage rectal cancer in patients. The main disadvantage of the TNM system is that it needs a specimen. It is a postoperative process for a disease for which preoperative decision making is crucial. In addition, it does not incorporate CRM, which is an established surrogate marker for LR and survival. Furthermore, it is based on studies of otherwise not treated surgical specimens. Its use after preoperative RT or CRT has not been evaluated fully. Moreover, TNM is staging from inside-out (from the lumen toward perirectal fat), whereas preoperative MRI-based staging is from outside-in (from the fascia toward the limit of the tumor as CRM).

Nevertheless, preoperative staging based on TNM is performed routinely. Concerning tumor (T) stage, there are 2 main issues. First, tumors of the distal rectum that are characterized as T1 are amenable to local excision and do not need administration of preoperative CRT. Second, the differentiation between T2 and T3 tumors often is difficult and MRI is not always reliable in that respect.

Nodal (N) staging is notoriously inaccurate by CT or even MRI because the lymph node size is not an accurate predictor of tumor involvement. Bipat et al. in a well-conducted meta-analysis concerning local staging of rectal cancer, showed that the sensitivity and specificity of endorectal ultrasound (EUS) for muscularis propria invasion, and therefore T staging, were superior compared with pelvic MRI. Lymph node involvement, however, was not at all satisfactory because the sensitivity and specificity decreased sharply to 67% and 78%, respectively. In addition, EUS can be used only for the evaluation of mesorectal lymph nodes and does not provide any information about lymph nodes outside the TME specimen. Furthermore, EUS is surgeon-dependent and cannot be used for the evaluation of stenotic tumors. EUS also is unable to depict CRM, which is a major drawback concerning its use in the preoperative planning of rectal cancer preoperative RT and surgery. The detection of distant metastases (M) is performed routinely to ascertain that the disease is locoregional. TNM staging, although important, currently is not used for preoperative decision making to the extent of the past.

The achievement of a free CRM is the main goal in rectal cancer treatment. An involved margin cannot be addressed by a second surgery, as is possible in breast cancer. This is why the preoperative planning is crucial in the management of rectal cancer. The CRM may be involved even in an intact mesorectal specimen because of perfect surgery but...
inadequate preoperative staging, that is, CRM is threatened in the first place. This mode of management still will lead to a significantly increased LR rate. Although numerous predictors of LR have been reported, the main factor is the involvement of CRM. Positive CRM is defined as the presence of tumor cells 2 mm from the edge of the resected specimen. CRM less than 2 mm has a detrimental effect on a patient’s LR rate and survival. The data from the Dutch study suggest that CRM less than 2 mm should be referred to as an involved margin because the LR in this group of patients was significantly higher (16% vs 6% in the group with CRM >2 mm). Nagtegaal et al also proposed the 2-mm as the limit for the involvement of CRM. A free CRM of at least 1 mm can be predicted when the measured distance on MRI is at least 5 mm, and a margin of at least 2 mm when the MRI distance is at least 6 mm.

Positive lymph nodes in the resected specimen traditionally are associated with increased LR. The TME concept argues that when the tumor is removed en bloc with its vascular supply and lymphatic drainage along the proper planes and with a clear CRM the nodal status does not affect the LR rate significantly.

The percentage of positive CRM and hence of LR rate is higher for abdominoperineal resections compared with anterior resections. This is a result of the minimal amount of fatty tissue around the lower third of the rectum. At this level, the tumor easily reaches the anatomical boundaries of the pelvis and no longer is amenable to radical resection. This is recognized by the pathologist in the surgical specimen, which presents a waist at this level, especially when a classic APR has been performed and a little amount of sphincter muscle has been removed with the specimen. The multidisciplinary approach to rectal cancer dictates that such an event should be prevented by the preoperative analysis of the pelvic MRI, which can identify the problem. The proposed solution is the use of the long radiotherapy scheme and/or appropriately oriented surgical planning to identify such areas of possible positive margin and stay wide during the resection in order to avoid positive resection margins. The “cylindrical resection” proposed by Holm et al offers reduced rates of positive CRM but has not been adopted widely yet. The main issue for the surgeon and radiologist to address is whether a radical resection is feasible for the patient and if a free CRM can be achieved. The pelvic MRI provides all the necessary information to tackle this issue. Patients may be categorized into groups based on the predicted CRM status as follows: group 1, the primary tumor is in the upper rectum. These tumors are intraperitoneal and preoperative CRT offers no benefit. Tumors of the middle and distal rectum that are T1 according to preoperative MRI also included in this group and surgery—TME or local excision—without preoperative CRT is suggested. Group 2 includes patients with the primary tumor in the middle or distal rectum. According to MRI the CRM is free (>2 mm). The patient is considered a candidate for curative resection after the administration of the short scheme of CRT. Group 3 includes patients with a primary tumor that potentially has involved CRM (<2 mm). The patient is a candidate for the long scheme of CRT. Group 4 includes patients with a primary tumor that is T4 and possibly requires pelvic exenteration. The patient is considered a candidate for referral.

Administration of preoperative radiotherapy

Administration of the short scheme of CRT. The Dutch study clearly showed that the administration of the preoperative short scheme of RT further reduced LR rates after TME surgery. The short scheme of RT consists of 5 fractions of 500 cGy (5 x 500) for 2,500 cGy. The patient is subjected to surgery 3 to 4 days after the completion of the short scheme to minimize postoperative complications. The short scheme sterilizes the surgical margins of TME and prevents residual foci of cancer cells to establish. It is important to emphasize that the short scheme does not downstage the tumor, in that respect it cannot secure a threatened CRM. Its main indication is when the CRM is evaluated as free based on the preoperative pelvic MRI. If the CRM is compromised, the short scheme of CRT is contraindicated. Peeters et al recently published the long-term results of the Dutch study that showed no survival benefit after the use of the short scheme of RT, whereas the reduced rates of LR (5.6% vs 10.9%, P = .001) are maintained even after 6 years of follow-up evaluation.

Administration of the long radiotherapy scheme. The long scheme of RT consists of 4,500 to 5,060 cGy in daily fractions during 4 weeks followed by surgery 4 to 6 weeks after the completion of CRT. The main indication for the use of the long scheme of CRT is when the CRM is threatened according to preoperative MRI. The long scheme can downsize the tumor significantly and in that respect increases the likelihood of a radical resection. The aim is to downstage the tumor and to secure the threatened CRM. After the administration of the long scheme of CRT a new MRI (post-CRT) is advisable before radical resection. The reason is 2-fold. First, we can assess the effectiveness of CRT by evaluating the response of the tumor and measure CRM (post-CRT). Second, the medical oncologist will record the effectiveness of the drugs used and modify the postoperative chemotherapy regimen based on the in vivo response of the tumor.

Preoperative CRT is associated with early and late toxicity but Sauer et al showed that these problems are less severe with preoperative compared with postoperative CRT. In many specialized centers the case has been made for preoperative CRT because of its beneficial effect on CRM.

Local excision or TME

In rectal cancer, the option of local excision and adjuvant CRT is available in selected patients. Local excision is a...
feasible option to avoid major surgery for distal rectal cancer. Pelvic MRI analysis and the characteristics of the tumor available from the preoperative biopsy can help in recognizing these selected cases in which local excision and avoidance of major surgical intervention is available. T1 tumors with no lymph node involvement can be cured by local excision alone. Patients unfit for surgery could be offered the option of local excision plus CRT even for T2 tumors. Transrectal ultrasound is needed for accurate staging of the tumor before local excision. It accurately can dictate the T stage of the tumor and identify the candidates for local excision. Nevertheless, transrectal ultrasound is surgeon-dependent and technically demanding. The MDT, based on imaging and after taking into account the general condition of the patient, needs to decide whether a radical surgery is warranted or local excision plus adjuvant CRT is a viable option.

Algorithm for the treatment of rectal cancer

Multidisciplinary treatment of rectal cancer consists of accurate imaging, meticulous surgery, and wise use of CRT. These elements are interconnected. Recently, Heald proposed a 6-stage process for the management of rectal cancer after establishing its diagnosis and excluding systemic disease (Table 2). In the first stage, a phased-array-coil, fine-slice, pelvic MRI is performed, which provides the essential elements for the preoperative decision making for rectal cancer. In the next stage, the MDT discusses the patient’s case and the overall treatment plan is formed. In stage 3, preoperative CRT is administered when indicated. Selection for preoperative CRT principally is according to preoperative MRI. In the fourth stage, a detailed precise surgical procedure is performed according to TME concept. In stage 5, pathologic audit of the specimen based on the Quirke protocol is performed postoperatively. Finally, the case is evaluated thoroughly within the MDT and decisions regarding postoperative treatment are made along with surgical audit and feedback from the pathologists.

The MDT is responsible for choosing the tailor-made management for all patients with rectal cancer and has to form an algorithm for the treatment of rectal cancer that is the backbone for any preoperative decision making for rectal cancer. The aim of the MDT is to improve results and to offer state-of-the-art treatment. We consider MDT discusssion obligatory for all patients with rectal cancer. The proposed algorithm (Fig. 1) is in favor of preoperative CRT for all patients with rectal cancer. The advantages of this approach in terms of LR and rate of complications are supported by recent prospective randomized trials. Reduced compliance and cancelation of postoperative CRT owing to medical reasons are avoided.

Acknowledgment

The authors thank Mrs E. Bolbasis for linguistic review and Assistant Professor K. Vagianos for critical review of this manuscript.

Table 2 Six-stage process for management of locoregional rectal cancer according to Heald

<table>
<thead>
<tr>
<th>Stage 1: pelvic MRI</th>
<th>Stage 2: MDT discussion</th>
<th>Stage 3: preoperative chemoradiotherapy when indicated</th>
<th>Stage 4: surgery according to TME concept</th>
<th>Stage 5: pathologic audit of the specimen based on the Quirke protocol</th>
<th>Stage 6: MDT decision regarding postoperative treatment</th>
</tr>
</thead>
</table>

References
