The diagnosis and management of rectal cancer: expert discussion and recommendations derived from the 9th World Congress on Gastrointestinal Cancer, Barcelona, 2007


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Knowledge of the biology and management of rectal cancer continues to improve. A multidisciplinary approach to a patient with rectal cancer by an experienced expert team is mandatory, to assure optimal diagnosis and staging, surgery, selection of the appropriate neo-adjuvant and adjuvant strategy and chemotherapeutic management. Moreover, optimal symptom management also requires a dedicated team of health care professionals. The introduction of total mesorectal excision has been associated with a decrease in the rate of local failure after surgery. High quality surgery and the achievement of pathological measures of quality are a prerequisite to adequate locoregional control. There are now randomized data in favour of chemoradiotherapy or short course radiotherapy in the preoperative setting. Preoperative chemoradiotherapy is more beneficial and has less toxicity for patients with resectable rectal cancer than postoperative chemoradiotherapy. Furthermore chemoradiotherapy leads also to downsizing of locally advanced rectal cancer. New strategies that decrease the likelihood of distant metastases after initial treatment need be developed with high priority. Those involved in the care for patients with rectal cancer should be encouraged to participate in well-designed clinical trials, to increase the evidence-based knowledge and to make further progress. Health care workers involved in the care of rectal cancer patients should be encouraged to adopt quality control processes leading to increased expertise.

Key words: rectal cancer, surgery, chemotherapy, radiotherapy

Rectal cancer is a common malignancy leading to high morbidity and considerable mortality. The evolution of the multidisciplinary management of rectal cancer has resulted in high local control rates, improved overall survival rates and improvement in the quality of life. Surgical resection is the cornerstone of the multidisciplinary approach of patients with rectal cancer. However, a curative resection for locally advanced cancer cannot always be achieved even with high-quality surgery, and local relapse or metastases still occur [1]. Hence, modern multimodal treatment of rectal cancer attempts to integrate surgery, radiotherapy and chemotherapy, and uses the expertise and knowledge of pathology and radiology. Multidisciplinary teams achieve the best results in terms of relapse rate, survival and quality of life [2–4]. Several excellent clinical guidelines and reviews have been published on rectal cancer. However, in this rapidly evolving field, new data frequently become available which form the rationale for this manuscript. These focus on the diagnosis and
treatment of rectal cancer and on the additional pre- or postoperative treatment.

This article summarizes the expert discussion on the management of rectal cancer, which was organized during the 9th World Congress on Gastrointestinal Cancer in June 2007 in Barcelona, Spain. Opinion leaders and experts from different nations, selected on scientific merit, participated in the discussion. In preparation of this expert panel, a detailed survey and questionnaire were sent to the panel and the questions, answers and conclusions were discussed at the meeting.

Expert committee reports reflect clinical experience in addition to evidence-based medicine. Therefore, agreement or consensus is not always reached. The main strength, however, of this approach is that it builds the framework for more than minimal guidelines for clinicians dealing with the difficult task of making treatment choices in their daily clinical practice.

**anatomical definitions**

The rectum extends from the recto-sigmoid junction to the anorectal ring. The proximal aspect is usually categorized in clinical trials as 12–15 cm from the anal verge. Cancers above this level are defined as sigmoid and are treated as colon cancers. This anatomical definition is, unfortunately, a crude measure. The rectum is defined as being at or below the peritoneal reflection, but the location of the reflection is variable with differences between female and male patients. Traditionally, tumours are measured with a rigid rectosigmoidoscope, since evaluation with flexible sigmoidoscopy or colonoscopy is not always reliable. The anal verge should be the anatomical landmark. The distance between the lower edge of the tumour and the anal verge is important for treatment stratification because it can influence the type of neo-adjuvant treatment, the type of surgery and ultimately, the outcome [5].

For international benchmarking, rectal tumours can be categorized according to their distal edge as ‘low’ (up to 5.0 cm above the anal verge), ‘mid’ (from 5.1 to 10.0 cm above the anal verge) and ‘high’ (from 10.1 to 15.0 cm above the anal verge).

A definition based on modern imaging is, however, more accurate and objective, and provides a more functional definition than a real anatomic definition. Based on spiral computed tomography (CT) scan and magnetic resonance imaging (MRI) the rectum is defined as being below the 1st or 2nd sacral vertebra (S1 and S2) [6–7].

An understanding of the embryological development of the rectum is helpful in optimizing the surgical management and minimizing the risks of local recurrence. The mesorectum is enclosed by the mesorectal fascia, an embryological remnant of the hind-gut containing the rectum and its associated lymph nodes and vasculature, in a complete anatomical space, providing a natural boundary for the tumour [1].

**staging**

The TNM classification of tumours described by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) is used for tumour staging [8]:

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<th>cTNM: pre-treatment clinical classification, based on clinical examination, imaging, endoscopy, biopsy, surgical exploration or other; pTNM: post-surgical histopathological classification; ypTNM: post-surgical histopathological classification following preoperative therapy (radio- and/or chemotherapy).</th>
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<th>N – Regional lymph nodes</th>
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diagnosis and pre-treatment staging of rectal cancer

The pre-treatment evaluation and staging are essential in determining the ideal surgical approach to rectal cancer as well as the sequencing of the various treatment modalities: radiation, chemotherapy and surgery. The exact definitions of the extent of local involvement and of the presence or absence of systemic disease are the most critical factors.

The diagnosis should be based on the results of the pathologic examination of biopsies, which must be obtained from all rectal tumours prior the start of any type of treatment. At diagnosis, a detailed family history should be performed. Clinical determination of the local extent of disease includes physical examination, including digital rectal examination. For experienced practitioners, digital rectal examination is reasonably accurate in assessing the distance between the rectal tumour and the anal verge as well as the depth of the rectal wall penetration, but not the lymph node status. The initial clinical evaluation also includes a pre-treatment functional scoring which will influence the therapeutic decision, especially in the elderly population. The functional scoring is based on a general functional evaluation as well as on a more specific evaluation of sphincter function. All patients with a rectal tumour should undergo a total colonoscopy to identify metachronous polyps or tumours.

Laboratory evaluation includes the evaluation of vital organ functions as well as the determination of CEA [9].

Further staging procedures should focus on the local extension/invasion, as well as identification of potential metastases. CT is part of the standard preoperative staging for rectal cancer. It has a good sensitivity in evaluating the presence of metastases. Therefore, a CT scan of the abdomen is mandatory in all patients with rectal cancer. A chest CT scan should also be performed in patients with lower and middle third rectal cancers and is recommended in patients with upper third rectal cancers, especially in more advanced tumours. The addition in cost of performing both abdominal and chest CT scans is limited and justifiable by benefits. The FDG-PET scan is only recommended in the setting of lesions in the liver or lungs which cannot be characterized, in order to rule out or to confirm the presence of metastases [10].

CT can also be used for assessing the involvement of adjacent organs by locally advanced tumours, but has limited accuracy in determining the T-stage of the tumours or the presence of nodal metastases. Several studies indicate that the accuracy of a CT for T-stage is 33–77% and 22–73% for nodal staging [5, 10, 11].

Endorectal ultrasound (EUS) is the most accurate preoperative staging tool for smaller rectal tumours. Several studies have shown that the overall accuracy for T-stage is 76–93% and for N-stage is 61–88%. EUS, however, is less accurate in the evaluation of the circumferential margin. EUS is thus most useful for patients with relatively small and early stage tumours. EUS is, however, operator and machine dependent, is more difficult to perform for high rectal tumours and is impossible in stenosing cancers [5]. Therefore, MRI can be advocated in this setting. MRI can predict with very high accuracy a clear or invaded circumferential resection margin (CRM) which may result from any involvement or breach of the mesorectal fascia. Some authors state that a distance of <3 mm between the tumour and the mesorectal fascia constitutes a positive potential CRM. In contrast many other experts accept that >1 mm distance between the tumour and the mesorectal fascia is adequate to predict a potentially negative CRM [6, 7, 12–14].

CT, MRI and EUS are not completely reliable for detection of lymph node involvement. However, contrast enhanced multislice CT may become a valid alternative. UPSIO-MRI is a promising, but still investigational, technique for the detection of a regional lymph node metastasis in rectal cancer [15]. Based on this information, phased array high resolution magnetic imaging (HR-MRI) is recommended, especially in patients with larger rectal cancers and/or stenosing rectal cancers to evaluate the circumferential section margin, to confirm the T-stage (especially T3/T4) and the N-stage. For identification of transmural penetration (T3 or more) and node positivity, it is recommended to use two staging/imaging modalities (EUS and HR-MRI or EUS and multislice CT).

For clinical decision making, particularly related to neo-adjuvant treatment, it is recommended to use the highest tumour or nodal category found by any of the imaging modalities.

Diagnostic imaging and its accuracy should always be discussed by a multidisciplinary team.

Specific issues and remarks in relation to staging:

- phased array MRI is the best method to assess the CRM;
- in proximal rectal cancer and in rectosigmoid cancer, staging is usually performed as in sigmoid cancer. In most patients a spiral CT-scan gives adequate information for an accurate treatment strategy;
- the definition of non-resectable rectal cancer is a multidisciplinary team decision. Non-resectability of a rectal cancer can be defined as a clinically fixed tumour, a tumour with a CRM = 0 or invasion of surrounding organs, a rectal cancer invading the pelvic sidewall or other cancers where performing a R0 resection is deemed impossible by the multidisciplinary team including the surgeon;
- many historic definitions (e.g. locally advanced rectal cancer) need now be challenged due to the evolution in preoperative staging and preoperative therapy. The finding of a threatened or not-threatened CRM will ultimately determine the preoperative treatment.
surgical management of rectal cancer

High-quality surgery is the cornerstone of the treatment in patients with rectal cancer. Preferably, surgery should be done by a team of experienced surgeons collaborating with a multidisciplinary team in high-volume centres. A correlation between the volume of the centre and the outcome has been reported and is accepted by the experts [4, 16].

The main goal of surgery is to obtain clear surgical margins yielding a curative R0 resection. The term curative resection should be based on histological confirmation of complete excision of the tumour with negative margins (proximal, distal and radial). Total mesorectal excision (TME) has become the standard procedure for mid- and low rectal tumours (Figure 1). It results in higher local control and increased disease free survival. The technique of TME is derived from the concept of the ‘holy plane’. The mesorectum is the embryological hind gut mesentery, consisting of fat, rectal venous and lymphatic drainage and the descending branches of the superior rectal artery. This structure should be removed along with the rectum, by dissecting in the fatty tissue that lies between the mesorectal fascia and parietal pelvic fascia, the so-called ‘holy plane’. For proximal rectal cancer, a ‘high’ TME, down to 5 cm below the cancer is recommended. The implementation of TME has led to a decrease in the abdomino-perineal resection rate. Histopathological assessment has shown that tumour invasion is mainly circumferential and not longitudinal. It is therefore accepted that if a distal clearance of 1 cm can be achieved, a low rectal cancer may be suitable for sphincter-preserving surgery or intersphincteric resection with reliance on the anal sphincter complex to preserve continence. Every effort should be done to maintain the sphincter function, provided that an oncologically appropriate intervention is performed [1, 17–20].

Whether neo-adjuvant chemoradiotherapy increases the number of sphincter-saving operations remains controversial. Many feel that neo-adjuvant chemoradiotherapy does not necessarily increase sphincter-saving operations, although data from randomized trials and the experience of some surgeons suggest that neo-adjuvant chemoradiotherapy may increase the chance of a sphincter-saving operation.

Lateral lymphatic dissection (D3-resection) without preoperative radiotherapy is often performed by Japanese surgeons, but is not the standard intervention in Western countries where preoperative irradiation of the lateral pelvic lymph nodes is usually performed. The major morbidity of a lateral lymphatic dissection is the risk for damage to the pelvic nerves with urinary and sexual impairment. Care should always be taken for preservation of the autonomic nerves and plexus [4].

Requiring examination of a certain number of lymph nodes (e.g. 12) is not feasible after preoperative radiotherapy or chemoradiotherapy, since the number of recovered lymph nodes is usually lower after neo-adjuvant treatment [1, 21–23]. Adequate quality control of the surgical and pathological specimens is always required.

Laparoscopic rectal resection is an option, provided the quality of the surgery is similar. An experienced surgeon in laparoscopic rectal surgery is needed to produce good results. Local excision and transanal endoscopic microsurgical resection (TEMS) are attractive techniques because of the low morbidity and functional sequelae as compared to a radical resection. However, the primary curative goal of surgery cannot always be achieved through these techniques. Decisions should be based on the patient history, comorbidities and tumour status at presentation. Local excision classically has been restricted to low risk pT1 rectal cancer. The transanal approach is technically suitable for tumours located in the lower third of the rectum (up to 7 cm), uT1N0, and tumours with a diameter of <3 cm. In contrast with local excision, TEMS allows a transluminal excision of a small rectal tumour at any level in the rectum up to 15 cm. In case of unfavourable pathologic findings (e.g. G3, lymphatic or vascular invasion) or positive margins, more radical surgery should follow immediately. These techniques remain controversial for T1 tumours invading the middle third or the deepest third of the submucosa (sm2 and sm3) [24–27].

neo-adjuvant treatment of resectable rectal cancer

A variety of different neo-adjuvant approaches has been proposed, mostly depending on the stage of disease [28–40].

In larger tumours (cT3-4 and/or N+) in which the goal is downsizing or downstaging, full course preoperative chemoradiotherapy (50.4 Gy plus concurrent chemotherapy) is standard treatment. In patients with tumours at earlier stages, where downsizing or downstaging are less important, two strategies can be advocated: preoperative chemoradiotherapy followed by surgery at 6–8 weeks, or short course radiotherapy immediately followed by surgery. Preoperative chemoradiotherapy treatment is clearly preferred over postoperative chemoradiotherapy [28–40]. Optimal staging is essential for a sound therapeutic decision.

Patients with a cT3N0, cT4N0 and cTxN+ should be considered for a neo-adjuvant chemoradiotherapy. According to most experts, T2N0 distal rectal cancer should also be considered also for a neo-adjuvant chemoradiotherapy. Indeed, in patients with low rectal cancer (0–5 cm from the anal verge) the risk of a positive CRM is higher and so is the rate of local recurrence. With the strategy of preoperative chemoradiotherapy or radiotherapy we probably overtreat some cT3N0 patients because of overstaging in some patients, but experts agree to take this risk as preoperative chemoradiotherapy is clearly better tolerated and results in a lower regional recurrence rate compared with postoperative radiotherapy or postoperative chemoradiotherapy.
Recent randomized studies in resectable T3/T4 rectal cancers have tested preoperative chemoradiotherapy and 5-FU-based chemotherapy versus radiotherapy alone [32, 33]. The addition of 5-FU based chemotherapy to preoperative radiotherapy increases the pCR compared to radiotherapy alone and provides evidence for improvements in local regional control. However, it has not translated into an improvement in disease-free and overall survival. The rate of sphincter-saving procedures was also not influenced by the addition of chemotherapy in these studies. Inaccuracies in preoperative staging, no TME surgical quality assurance, use of bolus rather than continuous 5-FU administration during the radiotherapy and relatively poor compliance with pre- and postoperative chemotherapy, however, implicate certain problems in interpreting the results of these studies. Preoperative chemoradiation resulted in a higher acute grade 3 and 4 toxicity compared to radiotherapy alone; postoperative complications were not significantly different.

Whether preoperative chemoradiotherapy is better than postoperative chemoradiotherapy in patients with resectable rectal cancer has been answered by a German trial [31] comparing preoperative long course chemoradiation with a similar regimen given postoperatively. Both treatment modalities resulted in a similar overall survival rates and disease-free survival rate, but preoperative chemoradiation was associated with significantly less locoregional recurrences and less toxicity compared to postoperative chemoradiation. Also, compliance with preoperative chemoradiotherapy was significantly better than with postoperative treatment.

A short hypo-fractionated preoperative radiation of 25 Gy in 5 fractions without chemotherapy followed by surgery performed within a few days after completion of radiotherapy reduced local recurrence [36]. The Polish trial is the only randomized controlled trial that compared short course of preoperative radiotherapy with long course of chemoradiotherapy in patients with low T3-T4 rectal cancers [41–43]. The results should, however, be interpreted with caution because of several weaknesses of this trial. Although both regimens demonstrated comparable results in terms of patient outcome, the advantage of tumour regression and downstaging after a longer radiotherapy regimen combined with chemotherapy was confirmed. Despite significantly higher rates of tumour response after chemoradiotherapy, the number of sphincter-saving procedures was similar to that documented after the short course radiotherapy. Acute radiotherapy toxicity was higher after chemoradiotherapy, postoperative complications were slightly lower in this group and late toxicity rates were comparable [44].

The interval to surgery treatment is 6–8 weeks after preoperative chemoradiotherapy. After short course radiotherapy, immediate surgery is performed. Irradiation should be performed with a multiple beam technique. In the long course chemoradiotherapy regimens fractions of 1.8 Gy per day are used for a total dose of 45–50.4 Gy. In short course radiotherapy, a total dose of 25 Gy in 5 doses of 5 Gy per fraction is used. Intraoperative radiotherapy can be considered if cR0 resection is performed.

In most cases, chemotherapy when combined with radiotherapy remains fluoropyrimidine-based. Often a continuous infusion of 5-FU during the whole duration of the radiotherapy is recommended. Capecitabine during radiotherapy is a valid alternative. The addition of oxaliplatin to 5-FU or capecitabine is under active investigation in phase 3 studies and is usually reserved for patients with locally advanced rectal cancer treated on a clinical trial. Chemotherapy cannot be added in clinically meaningful doses to a short course radiotherapy of 5×5 Gy.

There is no evidence on the value of restaging after preoperative radiotherapy or chemoradiotherapy. Local restaging is not recommended routinely, as it will not change management and as the interpretation after radiotherapy or chemoradiotherapy (especially CT scan and EUS) is difficult. Restaging with MRI for patients that had initially borderline resectable rectal cancers can however be considered in selected cases, to determine the best strategy. A CT scan to exclude metastases should be considered in patients in whom the interval between the first CT scan and the time of surgery is long (>8 weeks).

### adjuvant chemotherapy

Most patients who received a preoperative radiotherapy or chemoradiotherapy are candidates for postoperative adjuvant chemotherapy. The initial staging before the administration of neo-adjuvant treatment should dictate the need for adjuvant chemotherapy. Patients with a clinical stage II or stage III rectal cancer are therefore considered candidates for postoperative chemotherapy. Adjuvant fluoropyrimidine-based chemotherapy is beneficial to patients that show downstaging (pT1-pT2) after preoperative chemoradiotherapy or radiotherapy. It is, however, not completely clear whether patients that had a complete response after the neo-adjuvant treatment should also be offered postoperative adjuvant chemotherapy [45].

Adjuvant infusional 5-FU/folinic acid or capecitabine for a period of 6 months is recommended. Oxaliplatin-based regimens as postoperative chemotherapy is considered by some experts, while waiting the results of phase III trials in rectal cancer and also in patients in whom 5-FU-based chemoradiotherapy did not lead to a tumour regression or downsizing. The duration is sometimes limited to 4 months, especially in patients who were exposed to a long course of preoperative chemoradiotherapy.

Adjuvant chemotherapy should not be started in the presence of inadequate postoperative recovery or pelvic septic complications and should start within 3 months after surgery.

In patients who did not receive neo-adjuvant radiotherapy or chemoradiotherapy, adjuvant treatment should be considered after radical resection of a stage II–III rectal cancer. Chemoradiotherapy is more efficacious in this setting than radiotherapy alone or chemotherapy alone. The tolerance of postoperative chemoradiotherapy is however less good than when delivered preoperatively. In the setting of postoperative chemoradiotherapy a long course RT (45–50.4 Gy in fractions of 1.8 Gy) regimen in combination with chemotherapy (protracted infusion of 5-FU or capecitabine) is usually administered [30].
Laser photocoagulation to control bleeding may be indicated in an endoscopic rectal stent in case of obstructive symptoms. Some patients with a proximal rectal tumour may benefit from endoscopic palliative intervention has clearly decreased today.

Although the number of patients benefiting from an endoscopic palliative intervention has clearly decreased today, depending on the localisation of the largest tumour load and on the spectrum of symptoms, can be proposed.

The addition of the targeted agents bevacizumab and cetuximab in combination with chemoradiotherapy is under active evaluation in rectal cancer.

treatment of metastatic rectal cancer

As patients with metastatic rectal cancer represent a very heterogeneous population, it is difficult to define a unique strategy. Metastatic rectal cancer represents a challenge to be addressed by a multidisciplinary team. Different options, depending on the localisation of the largest tumour load and on the spectrum of symptoms, can be proposed.

Commonly, chemotherapy is considered the initial strategy. However, timing of chemotherapy can be modulated depending on the patient status: In patients with small (or asymptomatic) primary tumour and bulky metastases chemotherapy is usually started, while in patients with clearly resectable rectal tumour, initial surgical resection of the primary tumour can be proposed. An alternative is the introduction of a stent or diverting colostomy before the start of chemotherapy. Because the outcome of these patients is usually determined by the evolution of the metastases, chemoradiotherapy may be indicated if local symptoms from the primary tumour cannot be adequately controlled by medical treatment and/or stenting.

If the primary tumour and the metastases are both resectable, a strategy in which the intention of treatment is curative should be adopted. In this situation a start with chemoradiotherapy (5-FU/FA or capecitabine and radiotherapy in patients able to tolerate it. Although not proven in randomized trials, this strategy may lead to a higher regression rate and thus a higher resectability rate. As the addition of oxaliplatin obviously increases toxicity, patients should be carefully selected.

The addition of the targeted agents bevacizumab and cetuximab in combination with chemoradiotherapy is under active evaluation in rectal cancer.

endoscopic treatment and palliation

Although the number of patients benefiting from an endoscopic palliative intervention has clearly decreased today, some patients with a proximal rectal tumour may benefit from an endoscopic rectal stent in case of obstructive symptoms. Laser photocoagulation to control bleeding may be indicated in patients with an extremely poor prognosis. Endoscopic palliative treatment modalities will benefit mainly patients with a short (<3 months) expected survival time. In patients with a longer survival other treatment modalities may be of greater benefit.

Endoscopic stenting can also be indicated as a bridge to a more definitive treatment: patients with an acute obstruction may be treated with a stent until elective surgery is performed. Palliative radiation is another option.

surveillance of patients with rectal cancer

The aim of follow-up is to detect local recurrence or metastases at a surgically curable or treatable stage and to detect new primary tumours. Patients that would be eligible for further treatment in case of recurrent disease must be offered intensive follow up.

The surveillance strategy in patients with rectal cancer is similar to those of patients with colon cancer and, in general, follows the published guidelines [46]. Standard follow-up should contain a history, physical examination, including digital examination, laboratory testing, radiologic testing and endoscopic surveillance. Patients with a more advanced rectal cancer should undergo a more intensive surveillance program than patients with a less advanced rectal cancer.

Clinical examinations, including measurement of CEA, are recommended every 3–6 months in the first 3 years.

Liver imaging is necessary since most metastases occur in the liver. Ultrasound is a well accepted imaging tool, but is less accurate than CT or MRI in diagnosing liver metastases. Patients with rectal cancer also develop often lung metastases. A CT scan of the chest and abdomen every 6–12 months is therefore recommended for patients at high risk of recurrence. Long term follow-up is mandatory. Recurrences in patients with rectal cancer do often occur later than in patients with colon cancer. The recommendation is therefore to follow patients for at least 5 years for local recurrence or metastases. However, patients who received adjuvant therapy are at risk for delayed local recurrences and some recommend follow-up for 10 years in those patients.

In addition, an endoscopic follow-up has to be performed: a total colonoscopy in the preoperative period and one year after resection is recommended. If this examination is normal, the next examination can be scheduled after 3 years and later after 3–5 years. In patients with a hereditary and familial predisposition more intensive follow-up with colonoscopy must be considered.

When recurrence or metastases are detected, a multidisciplinary discussion in expert centres is needed in order to determine the resectability of the recurrent disease.

future research

There are still many open questions for future research, which include the evaluation of the diagnostic modalities to determine appropriate therapeutic strategies. We need predictive and diagnostic tools to better select patients for treatment.
strategies in rectal cancer. Molecular characteristics of rectal cancer have to be determined. The evaluation of newer and more optimal treatment strategies is a priority: more active neo-adjuvant and adjuvant treatment strategies are needed to decrease the high metastases rate in patients with rectal cancer. In this regard the evaluation of new agents that can potentially prevent tumour recurrence or metastases is important. The evaluation of the functional outcome of patients after rectal cancer with surgery and other treatment modalities should also be a priority.

disclosures

The authors have declared no conflicts of interest.

references


