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ACR Appropriateness Criteria® Resectable Rectal Cancer

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Abstract

The management of resectable rectal cancer continues to be guided by clinical trials and advances in technique. Although surgical advances including total mesorectal excision continue to decrease rates of local recurrence, the management of locally advanced disease (T3-T4 or N+) benefits from a multimodality approach including neoadjuvant concomitant chemotherapy and radiation. Circumferential resection margin, which can be determined preoperatively via MRI, is prognostic. Toxicity associated with radiation therapy is decreased by placing the patient in the prone position on a belly board, however for patients who cannot tolerate prone positioning, IMRT decreases the volume of normal tissue irradiated. The use of IMRT requires knowledge of the patterns of spreads and anatomy. Clinical trials demonstrate high variability in target delineation without specific guidance demonstrating the need for peer review and the use of a consensus atlas. Concomitant with radiation, fluorouracil based chemotherapy remains the standard, and although toxicity is decreased with continuous infusion fluorouracil, oral capecitabine is non-inferior to the continuous infusion regimen. Additional chemotherapeutic agents, including oxaliplatin, continue to be investigated, however currently should only be utilized on clinical trials as increased toxicity and no definitive benefit has been demonstrated in clinical trials.

The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every two years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances where evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Keywords: Appropriateness criteria, Rectal cancer, Chemoradiotherapy, Radiotherapy, Chemotherapy

Summary of literature review

Background

The American Cancer Society estimates there will be 103,170 new cases of colorectal cancer in 2012 with 40,290 of those being located in the rectum [1]. Anatomically, the rectum begins above the dentate line, which marks the cephalad extent of the anal canal, and extends above the peritoneal reflection to the sigmoid colon. The location of the rectum deep in the pelvis with its tight confines complicates surgical resection, leading to an increased risk of local recurrence with surgical resection alone. Local and distant recurrence rates after non-total mesorectal excision (TME) surgery alone are as high as 40%-60% [2], thus warranting adjuvant therapy to improve local/regional control. Clinical trials have investigated the use of multimodality therapy to decrease the incidence of both local and distant recurrence. Historically, after surgical resection adjuvant therapy would be delivered if high-risk features were discovered upon pathologic examination of the surgical specimen. Subsequent investigation examined the role of neoadjuvant therapy, and most recently comparisons of these techniques have been published. This document summarizes the major clinical trials and the role for multimodality therapy.

In 2004, a randomized trial from Germany was published establishing a regimen of preoperative chemoradiotherapy and surgery followed by additional cycles of

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chemotherapy alone as the standard of care for clinical stages T3 or T4, or for node-positive rectal cancer [3]. Other clinical studies from the United States, Europe, and Asia have also influenced the treatment strategies for operable rectal cancer, as various approaches using preoperative or postoperative radiotherapy, with or without chemotherapy, have been examined. A summary of the major randomized clinical trials spanning the past several decades is provided below.

Prognostic factors

Overall survival (OS) is most affected by the extent of disease, with increasing depth of rectal wall penetration and lymph node involvement being harbingers of worse outcome. Tumor location appears to be important in rectal cancer, with low-lying tumors having a greater propensity for local recurrence. Histological tumor grade is prognostic, with poorly differentiated tumors having a worse prognosis. The signet ring cell and mucinous varieties also portend a less favorable outcome. The mucinous variety can be visualized via magnetic resonance imaging (MRI) defined by greater than 50% mucin in the tumor, and this variety has recently been shown to respond less favorably to neoadjuvant chemoradiation. The pathologic circumferential resection margin (CRM) has been demonstrated to be prognostic, and at least one retrospective series confirms decreased cancer-specific survival with a CRM ≤2 mm [4,5]. Additionally, the ypCRM status (after neoadjuvant chemoradiotherapy) is a significant risk factor for local recurrence [6]. High-quality surgery with pathological evaluation of TME specimens is associated with a decreased risk of local recurrence. A pathological review of specimens from the Medical Research Council/United Kingdom (MRC CR07) trial, which required TME, clearly demonstrates that excellent surgical technique is directly related to local recurrence [7]. Only 52% of the specimens demonstrated a "good" resection truly in the mesorectal plane, 34% were found to be "intermediate" in the intramesorectal plane, and 13% were "poor" involving the plane of the muscularis propria. The 3-year risk of local recurrence was directly related to quality of surgery, with high-quality surgery resulting in a lower recurrence. Importantly, all surgical groups, regardless of quality of resection, benefitted from neoadjuvant radiation therapy.

Dose

Preoperatively large radiotherapy portals covering the tumor, entire mesorectum, and lymph node regions at risk are typically treated to 45 Gy with a boost delivered to the tumor and presacral lymph nodes. The boost dose typically ranges in clinical trials from 5.4 to 9 Gy. The Radiation Therapy Oncology Group® (RTOG®) conducted a phase II study (R-0012) investigating combined-modality therapy with higher doses and hyperfractionation [8]. Higher doses were associated with a similar pathologic complete response (pCR) rate at the cost of increased grade 3-4 acute toxicity; thus, the standard remains 50.4 to 54 Gy.

Postoperative radiotherapy with or without chemotherapy

Several classic trials have examined the use of postoperative irradiation alone or in combination with chemotherapy; conducted by the Gastrointestinal Tumor Study Group (GITSG), the North Central Cancer Treatment Group (NCCTG), and the Norwegian Adjuvant Rectal Cancer Project Group, radiotherapy delivered with concurrent chemotherapy improved both local control and survival [9-11]. Subsequently, studies R-01 and R-02 by the National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated that the role of radiotherapy is primarily local control in the postoperative setting [12,13].

The method of administrating chemotherapy appears to be important in obtaining optimal results. Protracted venous infusion of 5-fluorouracil (5-FU) was found to be superior to bolus 5-FU, with a 45%-50% decrease in hematologic toxicity [14] and is considered to be a standard adjuvant therapy; more recent studies have investigated alternate means of optimizing chemotherapy [14-16]. The choice of early versus late radiotherapy with respect to chemotherapy may also be important according to the preliminary results of a recent randomized study [17] and warrants further investigation. Because neoadjuvant chemoradiotherapy is superior to postoperative delivery, in cases where chemoradiation is clearly indicated, cT3-4 or N + neoadjuvant delivery is preferred. (See Table 1 and Table 2.)

Preoperative radiotherapy with or without chemotherapy

Exploring the role of preoperative radiotherapy alone (25 Gy in 5 fractions), a Swedish trial showed improvements in both local control and survival that persisted at 13 years of follow-up [18,19]. Late toxicity with this hypofractionated regimen is substantial and includes an increased risk of small-bowel obstruction, abdominal pain, diarrhea, bleeding, and fistula formation [20,21].

Both the MRC CR07 trial and the Dutch Colorectal Cancer Group (CKVO 95-04) investigated the role of radiation therapy with high-quality TME surgery. The Dutch study randomized 1,805 eligible patients to either surgery alone or short course radiation therapy (5 x 5 Gy) followed by surgery, and concluded that the addition of radiation significantly decreases the rate of local recurrence at 2 years even with high-quality surgery ($P < 0.001$) [22]. The MRC CR07 study attempted to

Table 1 70-year-old woman staged with endorectal ultrasound (EUS), a T2NX rectal cancer at 3 cm from verge, final pathology was T3N1 status post abdominoperineal resection (APR), KPS ≥70

Treatment	Rating	Comments
Treatment Options		
RT + chemotherapy	9	
RT alone	2	
Chemotherapy alone	2	
If RT + Chemo: RT Dose to Primary		
45 Gy/1.8 Gy	6	
50.4 Gy/1.8 Gy	9	
54 Gy/1.8 Gy	8	If small bowel is completely excluded after 50.4 Gy.
59.4 Gy/1.8 Gy	3	If small bowel is completely excluded after 50.4 Gy.
Simulation		
Patient prone	9	Unless physically unable. If using IMRT technique, may prefer supine.
Small-bowel contrast at simulation	9	Not mandated with CT simulation.
Patient immobilized	9	
Use belly board	9	Only needed if prone.
Perineal scar marker	9	
Bladder full at simulation	7	
If RT + Chemo: RT Volume		
L5/S1 pelvis to include perineal scar	9	
L5/S1 pelvis to bottom of ischial tuberosity	1	
RT Technique		
3 or 4 field with photons	9	Depending on clinical situation.
AP/PA	1	
3 field with electron boost to perineum	3	
4 field with electron boost to perineum	3	
IMRT	6	May be appropriate depending on the clinical situation on a case-by-case basis. Enrollment in a clinical trial preferred.

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate.

select high risk patients to selectively treat with radiation therapy; 1,350 patients were randomized to either neoadjuvant short-course radiation therapy (5 x 5 Gy) or selective postoperative concurrent chemoradiation

Table 2 70-year-old woman staged with EUS, aT2NX rectal cancer with caudal extent located 9 cm from verge, final pathology was T3N1 status post low anterior resection (LAR), KPS ≥70

Treatment	Rating	Comments
Treatment Options		
RT + chemotherapy	9	
RT alone	2	
Chemotherapy alone	2	
If RT + Chemo: RT Dose to Primary		
45 Gy/1.8 Gy	6	
50.4 Gy/1.8 Gy	9	
54 Gy/1.8 Gy	8	If small bowel is completely excluded after 50.4 Gy.
59.4 Gy/1.8 Gy	3	If small bowel is completely excluded after 50.4 Gy.
Simulation		
Patient prone	9	Unless physically unable. If using IMRT technique, may prefer supine.
Small-bowel contrast at simulation	9	Not mandated with CT simulation.
Patient immobilized	9	
Use belly board	9	Only needed if prone.
Anal marker	9	
Bladder full at simulation	7	
If RT + Chemo: RT Volume		
L5/S1 pelvis to include anal marker	2	CT simulation preferred. Use CT to ensure margin on inferior extent of tumor. Technically, the field should extend 2-3 cm below the anastomosis on the CT.
L5/S1 pelvis to bottom of ischial tuberosity	5	CT simulation preferred. Bony landmark is an approximation. Use CT to ensure margin on inferior extent of tumor. Technically, the field should extend 2-3 cm below the anastomosis on the CT.
RT Technique		
3 or 4 field with photons	9	Depending on clinical situation.
AP/PA	1	
IMRT	6	May be appropriate depending on the clinical situation on a case-by-case basis. Enrollment in a clinical trial preferred.

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate.

therapy (45 Gy in 25 fractions with 5-FU) to those patients with CRM involvement (defined as ≤1 mm) [23]. Patients with resectable rectal cancer who received preoperative radiation had a decreased rate of local recurrence at 3 years compared to patients who received adjuvant long-term radiation therapy. Together, the CKVO 95-04 and MRC CR07 studies confirm that radiation improves local control even with TME surgical technique. Because of the toxicity of long-term radiation treatment and the inability to safely combine the hypofractionated radiotherapy regimen with systemic chemotherapy, this approach is rarely used in the United States or Southern Europe, but it is more common in Northern Europe [20].

Importantly, two trials from Europe have examined the role of incorporating concurrent chemotherapy with preoperative irradiation using standard radiotherapy fractionation, in keeping with the postoperative combined chemoradiotherapy model. Two studies — one by the European Organisation for Research and Treatment of Cancer (EORTC 22921), the other by the Fondation Francaise de Cancerologie Digestive (FFCD 9203) — demonstrated a significant improvement in local control, in the absence of a survival or sphincter-preservation benefit, with the addition of chemotherapy [24,25]. As expected, acute toxicity was increased with the addition of chemotherapy, as had been noted in the FFCD 9203 trial [25]. (See Table 3.)

Preoperative versus postoperative chemoradiotherapy

The important question of comparing preoperative versus postoperative chemoradiotherapy, as noted above, was addressed by a randomized trial from Germany. The preoperative regimen, as published by Sauer et al [3], was associated with significantly improved local control and increased sphincter-preservation rates with no differences in disease-free or OS. As surgical technique continues to improve, it becomes increasingly difficult to demonstrate a benefit in disease-free or OS. Neoadjuvant delivery also resulted in decreased rates of acute and chronic treatment toxicity, when compared to the postoperative approach. Another randomized trial (NSABP R03) exploring the same question in the United States was terminated early due to poor accrual. This study did not require TME, but it did show a trend towards improved survival, with a significant improvement in recurrence-free survival and disease-free survival [26]. Clinical response to the preoperative therapy was associated with significantly improved disease-free and OS [27]. The current standard of care in the United States is, therefore, to provide preoperative chemoradiotherapy, using standard radiotherapy fractionation and concurrent fluorouracil for clinical stage T3 or T4 or for node-positive rectal cancer.

Simulation

Physical positioning to displace the small bowel is a simple way of maximizing the therapeutic ratio. A comparative study shows that when a patient is placed prone, the use of a belly board combined with a full bladder reduces the volume of small bowel irradiated by 70% (about 100 cc) [28]. Use of intensity-modulated radiation therapy (IMRT) with supine positioning potentially obviates the geometric benefit of placing the patient in the prone position on a belly board, which is uncomfortable and presumably more difficult for the patient to tolerate. A retrospective study comparing prone or supine setup with daily image guidance versus a no-action-level protocol confirmed that prone positioning leads to a greater systematic error. However, the study noted increased random error with the supine position. Error was decreased with either setup using increased frequency of image guidance [29]. One study from the UK evaluated prone versus supine positioning in 19 consecutive patients and found the prone position did decrease dose to the small bowel, but primarily only in the low dose region of the dose-volume histogram [30]. At doses above 20 Gy, there was no appreciable difference between supine and prone positioning, lending support to the notion of using the supine position in patients who may not tolerate lying prone with a full bladder.

Timing of surgery

One of the major differences in the adjuvant trials from Europe versus those from the United States has been regarding the timing of surgery after chemoradiotherapy. The short-course regimens from Europe with surgery 1 week after completing radiotherapy have not allowed adequate time for downstaging, yet it appears that with a longer interval from neoadjuvant therapy to surgery downstaging may occur. In a retrospective review of patients treated with neoadjuvant chemoradiation followed by surgery with a time interval ≤7 weeks versus >7 weeks, the longer interval before surgery demonstrated an improved pCR and near-pCR rates as well as increased disease-free survival interval [31]. A primary concern with an extended interval from chemoradiotherapy to surgery is that tumor clonogens are afforded time for repopulation and potential spread. A delay to surgery beyond 12 weeks has been investigated in selected patients and appears to be safe without an increase in metastatic spread [32].

Infusional versus oral 5-FU

Since the advent of oral 5-FU, capecitabine, its equivalence has been called into question. A multitude of retrospective data exists with conflicting results. Several randomized phase III studies have recently been reported that add support to the use of capecitabine.

Table 3 60-year-old woman with circumferential lesion with caudal extent located 8 cm from verge. EUS stage T3N1. KPS. ≥70

Treatment	Rating	Comments
RT		
Preoperative RT + chemo	9	
Postoperative RT + chemo	3	
Preoperative RT alone	1	
Postoperative RT	1	
If Preoperative RT: RT Dose		
45 Gy/1.8 Gy	7	
50.4 Gy/1.8 Gy	9	
54 Gy/1.8 Gy	7	If small bowel is completely excluded after 50.4 Gy.
59.4 Gy/1.8 Gy	2	If small bowel is completely excluded after 50.4 Gy. For fixed lesions only.
5 Gy x 5	1	
Surgery		
LAR	9	
APR	1	Only if LAR is not technically possible.
If Postoperative RT: RT Dose		
45 Gy/1.8 Gy	6	
50.4 Gy/1.8 Gy	9	
54 Gy/1.8 Gy	8	If small bowel is completely excluded after 50.4 Gy.
59.4 Gy/1.8 Gy	3	If small bowel is completely excluded after 50.4 Gy. For fixed lesions only.
5 Gy x 5	1	
Simulation		
Patient prone	9	Unless physically unable. If using IMRT technique, may prefer supine.
Small-bowel contrast at simulation	9	Not mandated with CT simulation.
Patient immobilized	9	
Use belly board	9	Only needed if prone.
Anal marker	9	
Bladder full at simulation	7	
RT Technique		
3 or 4 field with photons	9	Depending on clinical situation.
IMRT	6	May be appropriate depending on the clinical situation on a case-by-case basis. Enrollment in a clinical trial preferred.

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate.

NSABP R-04 is a randomized trial of radiotherapy with concurrent chemotherapy investigating four different chemotherapy regimens (5-FU or oral capecitabine with or without oxaliplatin). Preliminary results have recently been reported and show no significant difference between the arms with respect to pCR, sphincter preservation, or downstaging. However, the addition of oxalaplatin was associated with a notable increase in grade 3 and 4 gastrointestinal (GI) toxicity [33]. Another randomized trial of 401 patients from Germany comparing infusional 5-FU versus oral capecitabine concurrent with neoadjuvant radiation therapy suggests different toxicity profiles between the two chemotherapy regimens with less leucopenia and increased hand-foot skin reactions associated with capecitabine. This noninferiority German study suggests that oral capecitabine is not inferior to infusional 5-FU, and is associated with an increased rate of ypN0 tumors demonstrating increased downstaging with the oral drug [34].

Current questions

The role of neoadjuvant chemoradiotherapy in resectable rectal cancer has been established, but the possibility of increasing the therapeutic gain via newer chemotherapeutic agents exists. Two large trials, the French ACCORD and the Italian STAR trial, both evaluate the role of oxaliplatin, which increases the efficacy of fluorouracil-based chemotherapy in treating colon cancer [35,36]. These trials clearly show an increase in toxicity with the addition of oxaliplatin with no apparent improvement in local response. This use of oxalaplatin is supported by the recent preliminary results from NSABP R-04, which showed no apparent benefit with the addition of oxalaplatin to neoadjuvant concurrent chemoradiotherapy. The use of IMRT with capecitabine and oxaliplatin is being examined in a phase II study (RTOG® 08-22), but the results are not yet available. The role of biologic agents in treating rectal cancer has not yet been established.

The role of additional adjuvant chemotherapy after chemoradiotherapy in either the neoadjuvant or adjuvant setting is also in question. Although it is clearly indicated with colon cancer, several large trials from Europe and a meta-analysis have failed to show any benefit. Adjuvant chemotherapy after either neoadjuvant or adjuvant chemoradiotherapy has remained the standard of care based on extrapolated data from colon cancer. A randomized trial was initiated to determine whether additional chemotherapy is necessary in rectal cancer, but unfortunately due to lack of clinical equipoise, the study failed to accrue and closed early. Analysis of the Surveillance, Epidemiology, and End Results (SEER) database comparing patients who received adjuvant chemotherapy with those who did not suggests that patients

Table 4 45-year-old woman with EUS staged T4N0, 4 cm lesion at 3 cm from verge with extensive involvement of the anal canal, KPS ≥70

Treatment	Rating	Comments
Treatment Options		
Preoperative RT + chemo followed by surgery	9	LAR if possible.
Preoperative RT followed by surgery	2	
Surgery followed by adjuvant treatment if pT3+ and/or LN+	1	
If Preoperative RT: RT Dose		
45 Gy/1.8 Gy	6	
50.4 Gy/1.8 Gy	9	
54 Gy/1.8 Gy	8	If small bowel is completely excluded after 50.4 Gy.
59.4 Gy/1.8 Gy	3	If small bowel is completely excluded after 50.4 Gy. For fixed lesions only.
5 Gy x 5	1	Will not provide sufficient downstaging.
Simulation		
Patient prone	9	If using IMRT technique, may prefer supine.
Small-bowel contrast at simulation	9	Not mandated with CT simulation.
Patient immobilized	9	
Use belly board	9	Only needed if prone.
Anal marker	9	
Bladder full at simulation	7	
If Preoperative RT: RT Volume		
Pelvis to L5/S1 + boost	8	
Pelvis to L5/S1 + inguinal LN + boost	9	With extensive involvement of anal canal.
RT Technique		
3 or 4 field with photons	9	Depending on clinical situation.
AP/PA	1	
3 field with electron boost to perineum	3	
4 field with electron boost to perineum	3	
IMRT	8	Using atlas for target delineation. Based on anal cancer data. May be helpful to treat inguinal lymph nodes and to reduce side effects.
If Preoperative RT + Chemo: Time between RT and Surgery		
2-4 weeks	2	
>4-6 weeks	5	
>6-8 weeks	8	
>8 weeks	5	Extended length of time without therapy is discouraged. Strongly encourage enrollment in clinical trial.

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate.

who are node positive may benefit from additional chemotherapy [37].

IMRT has a demonstrated benefit in the treatment of anal malignancies, with fewer treatment breaks presumed to be due to the decreased toxicity associated with more conformal dose delivery. The RTOG® launched a phase II study investigating the use of IMRT for T3-4N0-2 patients with capecitabine and oxaliplatin. The preliminary results, presented in abstract form only, revealed a trend towards decreased preoperative GI grade ≥2 toxicity when compared to RTOG® 0247 [38]. A recent single-institution retrospective review comparing IMRT to classic 3-field conventional radiotherapy demonstrated a significant decrease in GI toxicity grade ≥2 for patients receiving IMRT [39]. It is the consensus of the expert panel authoring this document that IMRT clearly decreases toxicity in the treatment of rectal cancer. Certain situations requiring larger treatment volumes such as postoperative therapy after an abdominoperineal resection (APR) or radiation of the inguinal nodes warrants a stronger recommendation for IMRT; however, there are concerns regarding delivery of IMRT outside the confines of a clinical trial. IMRT requires a greater knowledge of anatomic spread and understanding of the surrounding normal tissues and tolerances than the conventional 3-field pelvis treatment based on bony anatomy. This difficulty in contouring was clearly demonstrated in RTOG® 0529 where there were a significant number of inadequately contoured cases; however, due to a rapid review process, corrections were made prior to patient treatment. Multiple studies document the interobserver variability in target delineation with highly conformal therapy, and the need for guidance or aids in target delineation to avoid missing critical targets [40,41]. The need for education regarding IMRT volumes in the pelvis was addressed by consensus panel of experts convened by RTOG® to create an anorectal contouring atlas that helps delineate targets [42]. The preferred delivery for

IMRT is via clinical trials; however, when being performed outside of a clinical trial, the atlas and peer review through colleagues or an established review process is strongly recommended.

Patients with low-lying rectal tumors extending below the dentate line and with extensive involvement of the anal canal receive treatment resembling that used for anal cancer, including treatment of the external iliac and inguinal nodes based on patterns of lymph node drainage. Retrospective data from MD Anderson Cancer Center suggests that the inguinal spread of rectal cancer, even with involvement of the anal canal, may be a rare event and that prophylactic radiotherapy to the groin may be unnecessary [43]. This study defines patients having disease within 4 cm of the anal verge as having involvement of the anal canal, but it does not comment on extensive involvement with extension to the anal verge or margin. Further validation is necessary before omitting inguinal radiation therapy in patients with extensive involvement of the anal canal. (See Table 4.)

Need for future trial

Despite the published data from randomized trials that support the shift to preoperative chemoradiotherapy, a subset of patients will require surgical resection upfront for a variety of clinical reasons. A pooled analysis of five randomized clinical trials in the United States suggests that not all patients with resected tumors may require a trimodality (surgery, chemotherapy, radiotherapy) treatment approach. Patients with favorable or "intermediate-risk" (T3N0 or T1-2N1) tumors were found to have benefited equally from either postoperative chemoradiotherapy or chemotherapy alone [44,45]. Other data from the Memorial Sloan-Kettering Cancer Center (MSKCC) suggests that understaging may be a significant problem, as 22% of the patients in the trial who were cT3N0 were found to be pN + at the time of surgery [46].

A risk-adapted approach, selecting patients for minimal surgery based on their response to preoperative chemoradiotherapy has been investigated. Preliminary results from a recently reported small phase II trial by the American College of Surgeons Oncology Group (ACOSOG Z6041) suggests select patients who have a small cT2N0 tumor may be candidates for preoperative chemoradiotherapy followed by local excision rather than proctectomy [47]. The possibility of deferring or eliminating surgery for patients with a complete response to neoadjuvant chemoradiotherapy has also been suggested [48]. A future clinical study is warranted to validate the appropriateness of such risk-adapted treatment-minimization strategies.

For additional information on ACR Appropriateness Criteria®, refer to www.acr.org/ac.

Competing interests

As of August 19, 2011, Joseph Herman, MD reported "Nucletron, Genentech"
As of June 27, 2011, Prajnan Das, MD reported "Research Support – Genentech"
For the remaining authors none were declared.

Authors' contribution

WJ, CT, JM, MW, NA, WB, PD, KG, TH, SK, AAK, ACK, MB, WS, JZ, WS. All authors read and approved the final manuscript.
The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

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