ARS Appropriateness Criteria

LOCAL EXCISION IN RECTAL CANCER

EXPERT PANEL ON LOCAL EXCISION IN RECTAL CANCER:

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SUMMARY OF LITERATURE REVIEW

INTRODUCTION

Thirty- nine percent of patients diagnosed with rectal cancer present with what the American Joint Commission on Cancer (AJCC) considers stage I disease.[1] Historically these patients have been treated with low anterior resection (LAR) or abdominoperineal resection (APR) with excellent local control (LC) and survival rates.[2-4] Postulating that early-stage lesions may not warrant total mesorectal excision (TME) as well as acknowledging the mortality and morbidity of these invasive procedures, investigators have examined less morbid sphincter-sparing approaches such as local excision (LE). LE has been presented as an option to patients whose other comorbid conditions would not allow them to tolerate more extensive surgery. Advantages of LE include minimal morbidity and mortality, with more rapid recovery period.[5,6] Limitations of LE include lack of pathologic staging of lymph node micrometastases which are less likely to be identified by staging imaging in early rectal cancer.[7] In recent years there has been additional evidence supporting the use of LE.[8-13] Local transanal excision (TAE) has been typically recommended only for stage cT1N0 as defined by endorectal ultrasound (EUS) or magnetic resonance imaging (MRI) and conditional on specific patient selection criteria[14] (See Subtopic 2. Patient Selection). There has been growing interest in the use of neoadjuvant radiation therapy (RT) or chemoradiation (CRT) to improve outcomes for patients with T1 or T2 cancers undergoing LE. The interest in the use of neoadjuvant RT or CRT is also in extending the indications for less radical surgery to selected patients with early-stage cancers at increased risk for local recurrence (LR) or patients with severe comorbidities and T3 cancers who have a complete or near-complete response to preoperative therapy. A few prospective multi-institutional trials have investigated the efficacy of combined LE and RT or CRT for these patients.[15-18]

Workup

All patients should receive a full colonoscopy with biopsy, pathology review, proctoscopy, carcinoembryonic antigen, and computerized tomography (CT) of the chest, abdomen, and pelvis. Since depth of tumor invasion has been shown to be an independent predictor for lymph node metastases in rectal cancer[19], patients being considered for LE should have additional local staging to evaluate depth of penetration. EUS is 62%–92% accurate for T staging and 64%–88% accurate for N staging but is highly operator dependent.[20,21] However, EUS may be more accurate for staging T1 and T3 rectal tumors and less accurate for T2 tumors[22], indicating the need for incorporation of other modalities in the workup of patients who are being considered for LE.[23] Limitations of EUS for staging of rectal cancer include difficulty fully imaging high rectal tumors and tumor deposits, nodal involvement and vascular invasion beyond the immediate area of the primary tumor.[24,25] MRI is more commonly included in the staging workup for patients with rectal cancer. High spatial resolution MRI of the pelvis provides detailed anatomical information for locoregional staging, especially when the information to be gained may impact local treatment recommendations.[26] A 2004 meta-analysis demonstrated that EUS and MRI have similar sensitivities and specificities for evaluations of pelvic lymph nodes (67% and 78%; 66% and 76%, respectively).[27] Agreement between clinical and histopathological TN stages for rectal cancer was approximately 50% independent of tumor location. However, Stage II-III was correctly predicted in 69% whereas pathologic Stage I was over-staged in 35%.[28] Currently pelvic MRI is the preferred modality for local rectal cancer staging.

TOPIC 1.
CLINICAL CONDITION: LOCAL EXCISION IN RECTAL CANCER

Subtopic 1.
Surgical Techniques

There are 3 operative approaches for LE of a distal rectal lesion: 1.) TAE, 2.) posterior trans-sphincteric (York-Mason procedure), or 3.) posterior proctotomy (Kraske procedure). TAE is the most commonly used approach. Under direct visualization, the lesion is excised with a 1-cm margin including the perirectal fat. The mural defect is then closed. It is important to note that none of these procedures include lymph node evaluation. Transanal endoscopic microsurgery (TEM) allows locally complete excision of rectal neoplasms and has recently been evaluated for curative treatment of invasive cancer. Both TAE and TEM involve full-thickness excision performed perpendicularly through the rectal wall into the perirectal fat avoiding tumor fragmentation. Negative deep and mucosal margins of at least 3 mm are recommended. It is important to orient the specimen for pathologic examination, so pathologists can adequately localize adverse features such as positive margins, lymphovascular invasion (LVI) or perineural invasion (PNI), invasion into the deepest 1/3 of the submucosa, or poorly differentiated tumor. In a meta-analysis comparing TEM vs. TAE, there was no difference in complication

rate, but TEM was significantly more likely to yield negative margins and a non-fragmented specimen.[29] Further, recurrence was significantly reduced with TEM vs. TAE. Patient reported outcomes have revealed a temporary but reversible impact on quality of life (QOL) and anorectal function with TEM[30], and it has been found to be safe following CRT.[31-35]

Subtopic 2.
Patient Selection

Historically, the best candidates for LE include small cT1N0 (<3 cm), low-lying tumors confined to the muscularis propria as defined by EUS or MRI and conditional on specific criteria (see Variant 1). These inclusion criteria based on the work by Nash et al. specify that the T1 lesion should not invade the deepest 1/3 of the submucosa, be limited to ≤ 30% of the bowel circumference, ≤ 3 cm in size, with clear margins (>3 mm), without LVI or PNI, be mobile and within 8 cm of the anal verge, and may be identified following endoscopic polyp removal.[10] There should be no evidence of lymphadenopathy on pre-treatment imaging.

Patients with subclinical nodal metastases undergoing LE alone are at risk for LR. Advanced age[36], pathological features (large tumor size[36], high tumor grade[36], LVI, or PNI[37]), and deep invasion[38] have been shown to be independent predictors for lymph node metastases and may be useful in identifying patients who would benefit from adjuvant therapy in addition to LE or potentially completion TME.

Patients with positive margins after LE or piecemeal resections are at very high risk of LR and should be offered immediate radical surgery, i.e. TME with anterior resection or abdominoperineal resection performed via either a traditional open or laparoscopic approach. In general, patients with cT2 tumors have a sufficiently high risk of lymph node involvement to warrant consideration of neoadjuvant or adjuvant therapy if radical surgery is not performed (see Variant 2). Patients with tumors invading the muscularis propria (T3) are at very high risk (>30%) for LR following LE and should not be treated with LE alone but may be considered for neoadjuvant therapy followed by restaging and consideration of LE for nonsurgical candidates with complete or near complete tumor response (see Subtopic 4).

Subtopic 3.
Local Excision With or Without Adjuvant (Chemo)RT

Studies have reported LR rates of 7%–40% and 25%–62% for LE alone in T1 and T2 tumors, respectively.[10-12,39-47] There are increasing data to suggest the role of prognostic factors to select patients who are at risk for recurrence and may benefit from adjuvant treatment.[48] Tumor diameter[49], pathologic T stage and extent of submucosal invasion, high tumor grade, positive surgical margin, and PNI or LVI have been identified as independent predictors of recurrence following LE.[50-52] Hence patient and/or tumor specific characteristics may influence recommendations for adjuvant therapy and may be incorporated into algorithms proposed for the selection of patients to be treated with LE alone.

Although there are no randomized data comparing postoperative RT to observation, retrospective studies show that adjuvant RT may lower LR rates following LE for early stage rectal cancer to 10%–20%.[11,12,17,40,53,54] There are also studies evaluating the role of adjuvant CRT in patients with high-risk early rectal cancer following LE.[55,56] One study evaluated LR rates for 83 patients with either pT1 having tumor size ≥ 3 cm, and/or resection margin ≤ 3 mm, and/or LVI, and/or non-full thickness excision such as endoscopic mucosal resection or any pT2 tumor who received adjuvant pelvic RT (50.4 Gy in 28 fractions) and concurrent 5-fluorouracil (5-FU) and leucovorin. In this study 15 patients (18.1 %) had stage pT2 tumors, 22 (26.5 %) had a margin of ≥ 3 mm, and 21 (25.3 %) had tumors of ≥ 3 cm in size. Thirteen patients (15.7 %) had LVI. The 5-year overall survival (OS), locoregional relapse-free survival (RFS), and disease-free survival (DFS) rates for all patients were 94.9, 91.0, and 89.8 %, respectively. Multivariate analysis did not identify any significant factors for OS or locoregional RFS, but the only significant factor affecting DFS was the pT stage.[55] Nonrandomized prospective studies which included patients receiving adjuvant CRT include the initial phase II study by the Radiation Therapy Oncology Group (RTOG 89-02) assigned patients to observation (low-grade T1 tumors with negative margins) or CRT (54-65 Gy with 5-FU 1,000 mg/m2 IV d1-3, d29-31) based on post-excision pathology. LR rates were 7%, 8%, and 23% for T1, T2, and T3 tumors, respectively.[17] Another prospective study, Cancer and Leukemia Group B study (CALGB 8984) evaluated the role of LE with or without chemotherapy and RT in 177 patients with T1 and T2 adenocarcinomas of the rectum. T1 patients underwent LE followed by observation. T2 patients underwent LE followed by RT (54 Gy/30 fractions) and chemotherapy (5-FU 500 mg/m2 IV d1-3, d29-

31). At 48 months of median follow-up, the 6-year OS rate was 85%, and the DFS rate was 78% for all patients. Three of the 59 eligible T1 patients and seven of the 51 eligible T2 patients had experienced LR, corresponding to 10-year LF rates of 8 and 18%, respectively. It is important to note, however, that these were highly selected patients and that one-third of patients was excluded after surgery due to large tumor size and/or questionable margin status.[16]

There are review data which attempt to further evaluate the relative benefit of CRT added to LE. A systematic review of 22 studies including 804 patients with T1, T2 and T3 tumors (35.1%, 58.0%, and 6.9%, respectively) who underwent LE (77% TAE) and adjuvant CRT or RT demonstrated LR rates of 5.8% for pT1, 13.8% for pT2, and 33.7% for pT3 tumors with an overall median DFS of 88%.[57] A 2004-2014 National Cancer Database (NCDB) study including 4,822 patients with T2N0 rectal cancer, 4367 who underwent radical surgery, 242 who received CRT followed by LE, and 213 who received LE followed by CRT as the primary treatment. Five year OS was similar between the groups (76.1%, 79.7%, and 77.4%, respectively).[58] A meta-analysis including 14 studies including 405 patients with pT1/pT2 rectal cancer removed by TAE and followed by either adjuvant CRT and 7 studies including 130 patients who underwent completion TME demonstrated a LR rate of 14% versus 7%, respectively. In this study, recurrence rates after adjuvant CRT versus completion TME were 10% and 6% for T1 tumors, and 15% versus 10% for T2 tumors.[59] These studies support the use of adjuvant therapy in addition to LE of high-risk pT1 rectal adenocarcinomas with poor prognostic features and pT2 tumors.

Subtopic 4.
Local Excision Following Neoadjuvant Radiation With or Without Chemotherapy

Results for neoadjuvant RT with or without chemotherapy followed by LE for rectal cancer have also been reported. Data from retrospective studies[18,34,53,60-64] and prospective studies[15,32,33] have demonstrated safety and LR rates ranging from 2.0%–13.2%. Since LE alone is associated with a higher risk of LR and inferior OS for patients with >T1 rectal cancer, studies have aimed to evaluate the relative benefit of this approach. The Polish Colorectal Cancer Study Group performed a phase III study for patients with cT1-2N0M0 or borderline cT2/T3N0M0 < 4 cm rectal cancer were randomized to receive either 5 × 5 Gy to the whole pelvis plus 1 × 4 Gy external RT boost 1 week later or CRT (50.4 Gy in 28 fractions plus 3 × 1.8 Gy boost and 5-FU with leucovorin bolus). LE was performed 6-8 weeks later. Patients with ypT0-1R0 disease were observed. Completion TME was recommended for poor responders (46% with ypT1R1/ypT2-3). Of 61 randomized patients, 51 were appropriate for analysis; 29 in the short-course group and 22 in the CRT group. Complete pathologic response (pCR) was not statistically different and was observed in 66% of patients in the short-course group and in 86% in the CRT group. The median follow-up was 8.7 years. LR and OS rates at 10 years were worse for the short-course group (35% and 47%, respectively) compared to the CRT group (5% and 85%, respectively). In total, 22% ($n = 11$) of patients experienced LR including 7% (1 of 15) with cT1 disease, 22% (6 of 22) with cT2 and 445 (4 of 9) with cT2/T3. Seventy-three percent of LR occurred within 3 years of follow-up and 91% within 5 years. Of the 11 patients with local recurrence, all were intraluminal and salvage surgery was performed in 9 patients (82%); 7 patients underwent TME and two had a second LE because they refused TME or were deemed unfit. In the two patients remaining, salvage resection was not undertaken because of unresectable tumor or comorbidity.[65]

The American College of Surgeons Oncology Group (ACOSOG) Z6041 investigated the oncological and functional outcomes of neoadjuvant CRT and LE for patients with pretreatment stage T2N0 rectal cancer. In this single-arm phase 2 study, 79 patients with clinical T2N0 rectal adenocarcinoma staged by EUS or endorectal coil MRI, measuring less than 4 cm in greatest diameter, involving less than 40% of the circumference of the rectum, located within 8 cm of the anal verge, received neoadjuvant CRT (twice daily capecitabine 725 mg/m^2 days 1-14 and 22-35, with oxaliplatin 50 mg/m^2 on weeks 1, 2, 4, and 5), and RT 1.8 Gy to a dose of 45 Gy, followed by a boost of 5.4 Gy) followed by LE. Forty-four percent of patients achieved a pCR, and 64% of tumors were downstaged to ypT0-1. Approximately 5% of patients were found to have ypT3 tumors at the time of LE. All but one patient had negative margins. Two patients had no surgery, 1 underwent TME and 4 additional patients who completed protocol treatment had TME (1 with positive margin and 3 ypT3 tumors). The therapy was associated with 39% of patients developing grade ≥ 3 treatment-related complications (29% had grade 3 gastrointestinal toxicity). Due to higher than expected toxicity, capecitabine dose was reduced to 725mg/m^2 twice a day, 5 days/week, for 5 weeks, and the total dose of radiation was reduced to 50.4 Gy. Oxaliplatin dose was un-modified. With a median follow-up of 56 months, the estimated 3-year DFS for the intention-to-treat group was 88.2% and for the per-protocol group was 86.9%. The authors of this study concluded that data suggests that neoadjuvant CRT followed by LE might be considered as an organ-preserving alternative in carefully selected patients with clinically staged T2N0 tumors who refuse, or are not candidates for, transabdominal

resection.[15] Numerous additional studies support these findings.[54,62,66-68] Anorectal function and quality of life were assessed at enrollment (71 patients) and 1 year postoperatively (66 patients) for ACOSOG Z6041 using the Fecal Incontinence Severity Index, Fecal Incontinence Quality of Life scale, and Functional Assessment of Cancer Therapy-Colorectal Questionnaire. Chemoradiation followed by local excision had minimal impact on anorectal function 1 year after surgery and was associated with stable overall quality of life, with mixed effects on different subscales. Fecal Incontinence Quality of Life results were significantly worse in the lifestyle, coping/behavior, and embarrassment, but there were no differences in the Functional Assessment of Cancer Therapy overall score, but the physical well-being subscale was significantly worse and emotional well-being was improved after surgery.[69]

Neoadjuvant CRT was also evaluated in the prospective, randomized, multicenter French Research Group of Rectal Cancer Surgery-2 (GRECCAR-2) phase III trial which included 186 patients with pretreatment T2-3 rectal cancers < 8 cm from the anal verge, ≤ 4 cm, and without evidence of metastatic disease (N+ allowed) who received CRT (45 - 55 Gy and concurrent fluoropyrimidine). Following CRT 145 good clinical responders (residual tumor ≤ 2cm) were randomly assigned to LE (n = 74) or TME group (n = 71). In the local excision group, a completion TME was required in 26 patients (35%) due to tumor stage ypT2-3. Unfortunately, this study failed to show superiority of LE over TME in a composite outcome involving death, recurrence, morbidity, and side-effects at 2 years after surgery because many patients in the LE group received a completion TME, thus increasing their side effects and morbidity. Of the 89 patients who underwent TME the nodal positivity rate was 0% in the T0/T1 tumors and 8% in the T2 and T3 tumors, suggesting that many patients could have avoided TME. However better techniques may help identify patients who may be able to avoid TME.[70] (see Variant 3)

The degree of tumor response to neoadjuvant therapy is variable. In many cases patients without clinical evidence of persistent tumor following neoadjuvant treatment (complete clinical response, cCR) are found to have in pCR. The management of patients with a near-cCR to neoadjuvant therapy and the potential prognostic value of pCR to neoadjuvant therapy followed by LE for LR is a topic of current investigation. A systematic review was conducted to determine the oncological outcomes and morbidity of LE after neoadjuvant therapy incorporating 20 studies (14 cohort, 5 comparative cohort, and 1 randomized controlled trial), consisting of 1068 patients with pretreatment clinical stage T2 and T3 tumors accounting for 46.4% and 30.7% of cases, respectively. Long-course neoadjuvant RT (with or without chemotherapy) followed by LE was delivered in all the studies, except to a cohort of 64 patients who received short-course RT without chemotherapy. Pooled cCR rate was 45.8% and pooled pCR rate was 44.2%. At a median follow-up of 54 months, ypT0 tumors had a pooled LR rate of 4.0% and a median DFS median rate of 95.0%. For ypT1 tumors or higher pooled LR and median DFS rates were 21.9% and 68.0%. Pooled incidence of complications was 23.2%, with suture-line dehiscence observed in 9.9%. The results of this pooled analysis are limited by selection bias, limited sample sizes and study quality/design.[71] The multi-institutional Transanal Endoscopic Microsurgery (TEM) After Radiochemotherapy for Rectal Cancer (CARTS) prospectively evaluated the number of patients with minimal residual disease (ypT0-1) after neoadjuvant CRT and TEM for early stage rectal cancer. This study included 10 patients with pretreatment clinical stage T1N0, 29 patients with T2N0 and 16 patients with T3N0 in rectal cancer who received neoadjuvant CRT with planned TEM. Among 47 patients who had TEM, ypT0-1 disease was found in 30, ypT0 N1 in one, ypT2 in 15 and ypT3 in one. After median follow-up of 17 months, 4 LRs were observed, including 3 of 9 patients with ypT2 tumors who declined further surgery and with ypT1 disease.[72]

Restaging of patients being considered for LE following neoadjuvant therapy can be even more challenging using standard staging techniques. It is important to evaluate not only response in the primary tumor following neoadjuvant CRT when considering LE; draining lymph nodes should also be carefully reexamined. The importance of this concept is demonstrated in a retrospective study of 725 patients of which 51% had node positive disease at diagnosis based on CT, MRI, or EUS, for whom the incidence of lymph node metastases was 9.7% for ypT0 and 17.6% for ypT1 following neoadjuvant CRT and radical surgery.[73] One prospective multicenter study demonstrated that restaging MRI using lymph node-specific contrast (ultrasmall superparamagnetic iron oxide) interpreted by an experienced radiologist can select rectal cancer with low risk of undetected nodal metastases (negative predictive value = 0.9) following neoadjuvant CRT and may be useful in identifying candidates for LE.[74] A subsequent meta-analysis assessing this study and 13 other articles found nodal restaging accuracy to range from 60 to 88%, with a mean accuracy of 72%.[75] However, this study included articles that assessed nodes on the basis of size, morphologic criteria, or both, and since up to 15% of nodes <3 mm will be malignant it is not recommended that nodes are evaluated on the basis of size.[76] Other investigators have demonstrated that MRI can detect reductions in tumor volume following neoadjuvant therapy and that a

>75% tumor volume reduction ratio is significantly associated with a high pCR rate, which may identify patients who are candidates for LE following neoadjuvant CRT.[77] In a series of 36 patients who had an unrecognized complete response at the time of restaging after CRT, it was noted that overstaging was mainly due to residual mucosal abnormalities at endoscopy, mixed signal intensity of irregular fibrosis at T2-MRI, and diffusion restriction on DWI and suspicious lymph nodes. The authors concluded that presence of these features may not actually be associated with residual tumor.[78] To date, the best way to evaluate lymph nodes in the mesorectum following neoadjuvant therapy has not been clearly defined. The use of MRI to assess tumor response following CRT demonstrates promise in defining candidates for LE following neoadjuvant therapy.

Subtopic 5.
Comparisons Between Local Excision With or Without (Chemo)Radiation and Standard Resection
An analysis of data from >154,000 resected rectal cancer patients diagnosed from 1998 to 2010 from the NCDB study found that for T1 and T2 rectal cancer excised with proctectomy were associated with higher rates of tumor-free surgical margins compared with LE (95% versus 76% respectively). There was also a small but significant decrease in OS for the T1N0 group.[79] Other systematic reviews note patient heterogeneity included in the studies resulted in difficulty drawing conclusions when comparing the effectiveness of TEM and radical resection in the treatment of T1 and T2 rectal cancer. The 2016 systematic review published by Sajid et al. included 10 trials (942 patients) that were significantly diverse in stage and grade of rectal cancer and the use of neoadjuvant CRT. Results demonstrated a trend toward a higher risk of LR (odds ratio 2.78; $p < 0.003$) and overall recurrence ($p < 0.01$) following TEM compared with radical resection. The risk of distant recurrence, OS and mortality was similar. TEM was associated with a shorter operation time and hospital stay and a reduced risk of postoperative complications ($p < 0.0001$). Although TEM appeared to have clinically measurable advantages, firm conclusions could not be drawn.[80] Another meta-analysis comparing the efficacy of TEM compared to TME for treatment of T1 rectal cancer published by Lu et al. demonstrated that the distant metastasis, OS and DFS rates did not differ between TEM and TME, although the LR rate after TEM was higher compared to TME. This study included one randomized control trial and 6 non-randomized controlled trials (860 patients total with 557 treated with TME and 303 treated with TEM). LR rates were significantly different between TEM and TME (odds ratio 4.62; $p = 0.0003$).[81]

Subtopic 6.
Comparisons Between Local Excision and Standard Resection for Rectal Cancer
Three small randomized controlled trials including 25 to 50 patients per treatment arm have compared LE to radical resection for stage I rectal cancer demonstrating similar oncologic outcomes.[32,82,83] In addition, 3 meta-analyses have also compared LE to radical resection for this subset of patients.[84-86] A meta-analysis from Shaikh et al. reported 10-year OS compared LE to radical resection following neoadjuvant CRT including all disease stages. No differences in LR, OS and DFS were noted between LE and radical resection in the pooled analyses. Subgroup analyses were possible for LR and DFS for T3 tumors, also showing no worse outcomes with LE leading the authors to note this as an option for patients at high risk for radical surgery.[85] Another meta-analysis that did not include studies incorporating CRT reported unadjusted risk ratios for 5-year OS from 12 observational studies ranging from 0.11 to 2.87. This meta-analysis included 7 studies that compared TAE to radical resection and 5 studies that compared TEM to radical resection (risk ratios for 5-year survival 0.11–1.53). Although significantly worse OS was noted for those patients receiving LE, the TEM subgroup did not have worse OS compared to radical resection. Local resection was found to be associated with lower perioperative mortality, postoperative complications, and the need for a permanent stoma. The authors stated that results were not influenced by a higher proportion of tumors located in the lower third of the rectum because meta-regression in case of similar ratio of lower-third cancers was not significant. Five-year DFS risk ratios were reported in this study from 10 observational studies comparing local resection to radical resection ranged from 0.31 to 8.31.[84] An additional systematic review and meta-analysis evaluating the combination of the above Shaikh et al. and Kidane et al. studies showed no difference in OS or DFS between LE vs. radical resection for stage I rectal cancer (T1-T2, N0). In this study LR more frequently occurred after LE (relative risk = 1.90, 95% CI: 0.57–6.32) but significance was not reached because of the low event rate ($p = 0.30$). Secondary outcomes including blood loss, operative time, hospital duration, number of permanent stomas and perioperative mortality favored LE.[86] An additional meta-analysis compared outcomes for 121 patients with T2 rectal cancer who received TEM alone (n=59) or following neoadjuvant therapy (n=62) with 174 patients who were treated with TME. Although there were no significant differences in LR, overall recurrence or OS rates between the TME and TEM + neoadjuvant treatment groups, TEM without neoadjuvant therapy was associated with increased LR, overall recurrence, and shorter OS for patients with T2 low lying rectal cancer.[87] Similar results were observed in the NCDB analysis

evaluating outcomes for 4822 patients with T2N0 rectal cancer (4367 underwent radical surgery, 242 received CRT followed by LE, and 213 received LE followed by CRT). With a mean follow-up period of 48.6 months, there were no differences in 90-day mortality or 5-year OS.[58]

This topic continues to be evaluated in a non-inferiority multicenter prospective randomized controlled study of rectal cancer T2-T3s (superficial) N0, M0 undergoing neoadjuvant treatment and LE (TEM) vs. TME trial aims to demonstrate the organ preservation rate following preoperative CRT and TEM in rectal cancer (https://clinicaltrials.gov/ct2/show/NCT01308190). This prospective, multicenter, randomized controlled non-inferiority trial will include 173 patients with rectal adenocarcinoma less than 10 cm from the anal verge and up to 4 cm in size, randomized to either CRT with TEM or TME. Patients will also be followed for local and systemic relapse.[88]

Subtopic 7.
Non-Operative Management (NOM); The Watch and Wait Strategy Following CRT
Given the high rate of LR among incomplete responders in this population[63], future studies are focusing on predicting patients who will achieve pCR. The main challenge is selection of patients who can be considered for this approach. The evidence available comes mainly from retrospective data, which include patients with variable tumor characteristics and pretreatment clinical stage, many who have been evaluated with inaccurate and insufficient staging modalities. Habr-Gama et al. published a 26.8% cCR rate in rectal cancer patients who received CRT, which included 69% pretreatment clinical stage T3 tumors.[89] A retrospective study also published by Habr-Gama et al. assessing the outcomes of a watch and wait strategy for patients with cT2N0 rectal cancer located < 7 cm from the anal verge who received CRT. Patients were treated with 54 Gy and 6 cycles of 5FU-based chemotherapy or 50.4 Gy with 2 cycles of 5-FU-based chemotherapy. Those treated with higher doses of radiation were more likely to achieve a cCR (85.7 vs 56.6%, respectively; $p < 0.001$).[90] These data support consideration of treatment strategy of surveillance in patients with early-stage low cancers who achieve cCR. Other studies have demonstrated that non-operative management of patients with cCR following CRT results in better anorectal function in comparison with patients with near-complete response managed by TEM.[91,92] A recent publication examined the potential of organ preservation with LE or active surveillance following CRT for 362 patients with non-metastatic cT3 or any stage N+ locally advanced rectal cancers treated with neoadjuvant CRT evaluated for clinical response. Active watch and wait surveillance was offered to 10 patients who were found to have a cCR and TAE was performed in 50 patients who were found to have an objective clinical response with residual ulcer measuring <3 cm. Of the 60 patients offered LE or active surveillance an 8.9% LR rate was observed. There was no significant difference in OS or DFS however when the outcomes of radical surgery were compared with LE.[93]

A major challenge in selecting appropriate patients for the watch and wait strategy is the appropriate selection of patients suitable for this approach as not all patients who achieve cCR are found to have pCR. There is no consensus regarding the methods employed for reassessment as all are associated with limitations. Despite the selection of surveillance tools, an active surveillance protocol is necessary in all patients who are considered for the watch and wait approach which usually includes clinical examination, monitoring of CEA level, periodic flexible sigmoidoscopy and/or complete colonoscopy and imaging exams. No clear recommendation as to the best surveillance program has been defined, but most agree that patient should be evaluated very 1 to 3 months for at least the first 2 years, during which time most tumor recurrences will occur.

Controversy exists over the optimal interval between treatment completion and response assessment, which should ideally assess the greatest tumor regression, while considering the impact of time interval on salvage surgery, if necessary. Several retrospective studies have suggested a pCR rate when delaying surgery after neoadjuvant CRT.[94,95] Some studies performed reassessment at a fixed time points (6, 8 or 10 weeks)[93,96-99] while others assessed response at longer intervals (8 to 12 weeks).[100-102] Two NCDB studies and a meta-analysis designed to answer the question on optimal timing of surgery following neoadjuvant CRT in patients with pretreatment clinical state II and III rectal cancer suggested that an delaying surgery no less than 8 weeks following completion of neoadjuvant CRT provided an optimal resulted in the best rate of pCR and downstaging without increasing complications or morbidity.[103-105] In addition to these retrospective data, there is one prospective study that directly evaluated the effect of increasing the interval between the end of RCT and surgery on the pCR rate. The Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response In Rectal Cancer: A Multicenter, Randomized Controlled Trial (GRECCAR-6) study randomized 265 patients with cT3/T4 or Tx N+ tumors of the mid or lower

rectum who had received CRT (45 to 50 Gy with 5-FU or capecitabine) to 7-week or the 11-week intervals before surgery. The primary end point was the pCR rate defined as a ypT0N0 specimen and was not statistically different between the 2 groups (7 weeks: 20 of 133, 15.0% versus 11weeks: 23 of 132, 17.4%; $P = 0.5983$). Morbidity was significantly increased in the 11week group (44.5% versus 32%; $P = 0.0404$) which was also associated with worse quality of mesorectal resection (complete mesorectum (78.7% versus 90%; $P = 0.0156$). This study concluded that waiting 11 weeks after CRT did not increase the rate of pCR and may be associated with higher morbidity and more difficult surgical resection.[106] Although these studies do not directly address the optimal time to assess clinical response following neoadjuvant treatment to determine whether salvage surgery is necessary, these data provide information regarding the impact of time interval on surgical complications and outcomes which are important when considering the "watch and wait" approach.

Although this "watch and wait" approach continues to be an active topic of clinical investigation, radical surgery following CRT remains standard of care for patients with T3 tumors able to undergo surgery, and neoadjuvant CRT followed by LE should be considered only in a clinical trial setting. Currently, there is no level I evidence to support a watch and wait approach in patients achieving cCR after CRT for rectal adenocarcinoma. The Rectal Sparing Approach after preoperative Radio- and/or CHemotherapy (RESARCH) in patients with rectal cancer is a multicenter observational study to evaluate the effectiveness of rectum-sparing approaches at 2 years after the completion of neoadjuvant treatment (https://www.clinicaltrials.gov/ct2/show/NCT02710812). In this study patients with rectal cancer eligible to receive neoadjuvant CRT will be prospectively enrolled and restaged 7-8 weeks after the completion. Those patients with major clinical response (mCR) or cCR (defined as absence of mass, small mucosal irregularity no more than 2 cm in diameter at endoscopy and no metastatic nodes at MRI) will undergo LE, while patients with cCR will either undergo LE or watch and wait policy. The primary endpoint is to determine rectum preservation rate at 2 years.[107] The Deferral of Surgery trial (https://clinicaltrials.gov/ct2/show/NCT01047969), is a prospective study of the watch and wait approach in rectal cancer patients using a controlled surveillance program. This study is designed to estimate the percentage of patients who can safely omit surgery, defined as the percentage of patients at 2 years after completion of CRT who have not had surgery and who achieved cCR. This study uses digital rectal exam (DRE), CEA, MRI and FDG-PET at 8 weeks following completion of CRT to demonstrate absence of visible tumor which defines CCR. Flexible sigmoidoscopy and colonoscopy are performed periodically starting at 6 months, and CR is performed annually. Patients are reevaluated with CEA, DRE and MRI more frequently in the first 16 weeks after completion (every 4 weeks), every 3 moths up to 2 years, every 6 months from 2 to 5 years, then annually thereafter. Of note, biopsies are only indicated if regrowth is suspected and MRI and PET-CT are performed to reduce the rate of false-positive finding on imaging.

Subtopic 8.
Simulation, Treatment Technique, and Radiation Dose

Patients treated with 3-D conformal RT should be physically positioned at the time of simulation to displace the small bowel in order to minimize treatment toxicity, and small-bowel contrast can be used to assist in identification of small bowel for treatment planning purposes. The use of a belly board with the patient in prone position with a full bladder has been shown to reduce the volume of irradiated small bowel by approximately 70% (about 100 cc).[108] However, this position may be difficult for some patients to tolerate. Retrospective comparison of treatment in the prone versus supine position, with or without daily image guidance, demonstrates that prone positioning leads to a greater systematic error, whereas the supine position was associated with increased random error. However, the increased use of image guided radiation therapy (IGRT) was noted to decrease the setup error associated with supine positioning.[109] Another prospective study comparing treatment in the prone versus supine position demonstrated a primarily low-dose region of the dose-volume histogram for the small-bowel associated with the prone position, although there was no appreciable difference between supine and prone positioning in the volume of small bowel receiving higher doses (>20 Gy).[110] For consistency in regards to bladder filling, it is best to give the patient clear instructions (e.g. first empty bladder and then drink 16 oz of water 1 hour before simulation and each subsequent treatment). Clinicians should consider CT-based image guidance before RT to decrease PTV margins (e.g. 5 mm) and to provide patient feedback regarding consistency of bladder filling in addition to target coverage.

A 3-field or 4-field 3-D conformal treatment technique with prone setup using a belly board with or without full bladder to displace bowel from radiation field is an acceptable method of treatment. Likewise, 3-field or 4-field 3-D conformal radiation using a supine technique with careful attention to bowel in the field may be also acceptable

in patients who cannot tolerate the prone position. Although a 3-field approach using posterior-anterior and lateral fields are preferred to best avoid small bowel, for larger patients a more lightly weighted 4th anterior field may be appropriate to improve RT plan dose homogeneity.

A total radiation dose of 50 to 56 Gy should be used for patients T2 tumors or T1 tumors with high risk features and margins of at least 3mm. For patients with high risk features and close margins higher radiation doses may be considered. This recommendation is derived from RTOG 89-02 which included patients with rectal tumors $\leq$ 4 cm diameter and occupying 40% or less of the rectal circumference who were underwent local excision using transanal, trans-sacral, or transcoccygeal approach. Patients with the most favorable risk profiles remained under observation. Patients with high-risk features but at least 3 mm surgical margins received adjuvant RT to a total dose of 50–56 Gy plus two cycles of 5-FU (1,000 mg/m^2 over 96 hours). Patients with high-risk features and close or positive margins underwent similar treatment, but to a total RT dose of 59.4–65 Gy.[17] CALGB 8984 included 110 patients with T1 or T2 rectal tumors who underwent local excision with pathologically negative margins. Patients with T1 tumors underwent observation while those with T2 tumors received adjuvant RT to 54 Gy with 2 cycles of 5-FU (500 mg/m^2 over 72 hours). No statistical difference was observed between the T1 and T2 patients with respect to 6-year overall survival (87% vs. 85%) or failure-free survival (83% vs. 71%).[16]

SUMMARY OF RECOMMENDATIONS

- The panel recommends that LE alone may be an acceptable treatment strategy for uT1N0 rectal cancers without high-risk features associated with increased risk of recurrence
- The panel strongly recommends adjuvant RT or CRT for patients who undergo LE for T1N0 rectal cancers and have known clinical or pathological adverse risk factors.
- The panel recommends strongly that adjuvant or neoadjuvant therapy should be considered in patients treated with LE for T2N0 rectal cancers, which are associated with a higher risk of lymph node metastases.
- The panel recommends with reservation the use of MRI to assess tumor response in patients with early stage rectal cancers to define candidates appropriate for LE following neoadjuvant therapy.
- The panel does not recommend neoadjuvant therapy followed by restaging and LE for T3N0 rectal cancers with or near complete tumor response outside of a clinical trial. These patients with are at very high risk for nodal involvement and LR, and therefore the panel strongly recommends that TME following neoadjuvant CRT is the standard of care for curative intent treatment for those able to undergo this procedure.
- The panel does not recommend neoadjuvant therapy followed by a watch and wait approach in patients achieving CCR following CRT outside of a clinical trial setting.

Summary of Evidence

Of the 110 references cited in the ARS Appropriateness Criteria Local Excision in Rectal Cancer document, 73 of them are categorized as therapeutic references, including 7 well-designed studies, 50 good quality studies, and 16 studies that may have design limitations. There are 8 references that may not be useful as primary evidence. There are 11 references that are meta-analysis studies.

The 110 references cited in ARS Appropriateness Criteria Anal Cancer document were published from 1998 to 2018. Although there are references that report on studies with design limitations, 57 well-designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the ARS Appropriate Use Criteria methodology and other supporting documents go to http://www.americanradiumsociety.org/page/aucmethodology.

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Clinical Condition: **Local Excision in Rectal Cancer**

Variant 1: **57-year-old man with preoperative MRI staged cT1N0 freely mobile, moderately differentiated adenocarcinoma. Tumor is 2 cm in diameter, involves <25% of circumference, and is located 6 cm from anal verge. No lymphovascular space or perineural invasion is noted. CEA is normal.**

TREATMENT	Rating Category	Group Median Rating	SOE	SOR
Local Excision, pT1N0 and 4mm Negative Margins				
Observation	A	8	S	↑
Adjuvant RT Alone	U	3	S	↑
Adjuvant CRT	U	3	S	↑
Local Excision, pT1N0 and Positive Margins				
Observation	U	1.5	S	↑
LAR or APR	A	8	S	↑
Adjuvant RT Alone	M	4	S	↑
Adjuvant CRT	M	6	S	↑

***5-FU based CRT in combination with LE may be appropriate for patients who are medically inoperable or refusing to undergo LAR or APR**

KEY: RT = Radiotherapy; CRT = Chemoradiation; LAR = Low Anterior Resection; APR = Abdominoperineal Resection

Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Clinical Condition: **Local Excision in Rectal Cancer**

Variant 2: **65-year-old otherwise healthy woman with preoperative MRI staged cT2N0 moderately differentiated adenocarcinoma. Tumor is 3 cm in diameter, freely mobile, and is located 3 cm from anal verge without sphincter invasion. No lymphovascular space invasion is noted.**

TREATMENT	Rating Category	Group Median Rating	SOE	SOR
Treatment Options				
LAR or APR	A	8	S	↑
LE Alone	U	2	M	↑
LE followed by CRT*	M	5	M	↑
Neoadjuvant CRT followed by LE**	A	7	M	↑
LE followed by RT Alone	U	3	M	↑
If LE with RT or CRT: RT Dose				
45 Gy/1.8 Gy	M	4	M	↑
50.4 Gy/1.8 Gy	M	5	M	↑
45 - 50.4 Gy/1.8 Gy to the pelvis followed by a 5.4 - 9 Gy/1.8 Gy boost	A	8	M	-
Simulation				
Patient prone on belly board	A	8	S	↑
Supine	M	6	S	↑
Small-bowel contrast	A	7	M	↑
Patient immobilized	A	8	M	↑
Anal marker	A	8	EO	↑
Bladder full	A	8	S	↑
If LE with CRT: RT Volume				
Pelvis CTV and tumor GTV determined using CT/MRI; treatment to 2–3 cm proximal/distal to tumor	A	9	S	↑
Inclusive of internal iliac nodes	A	9	S	↑
Inclusive of external iliac nodes***	M	4	S	↑
Inclusive of inguinal nodes***	U	3	S	↑
Tumor bed alone with 2–3 cm proximal/distal margin	U	3	S	↑
Radiation Technique				
IMRT	M	6	S	↑
3 field with photons	A	8	S	↑
4 field with photons	M	5	S	↑
AP/PA	U	3	S	↓

***5-FU based CRT following LE may be appropriate for patients who are refusing to undergo LAR or APR**

****Neoadjuvant CRT + LE may be appropriate for carefully selected patients with excellent clinical response assessed by physical examination, endoscopy, and imaging**

*****Treatment of inguinal nodes and external iliac nodes may be considered for tumors with sphincter invasion**

****** IMRT may be appropriate in patients using supine position, especially those who are unable to lie prone**

KEY: LAR = Low Anterior Resection; APR = Abdominoperineal Resection; LE =Local Excision; CRT = Chemoradiation; RT = Radiotherapy; GTV = Gross Tumor Volume; CTV = Clinical Target Volume; IMRT = intensity modulated radiotherapy; AP/PA = anterior-posterior and posterior-anterior fields

Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Clinical Condition: **Local Excision in Rectal Cancer**

Variant 3: **60-year old woman with MRI staged cT3N0 adenocarcinoma located 4cm from anal verge, 3.5 cm in maximum dimension with 40% circumferential involvement. Surgeon recommended APR.**

TREATMENT	Rating Category	Group Median Rating	SOE	SOR
APR	M	6	S	↓
Neoadjuvant CRT followed by LAR or APR*	A	8	S	↑
Neoadjuvant CRT followed by LE**	M	4	M	↓
LE Alone	U	1	L	↓
LE followed by CRT	U	2	M	↓
Neoadjuvant CRT followed by Active Surveillance***	M	4	M	↓

***LAR or APR should be used in patients with poor response or stable disease following neoadjuvant therapy as assessed by physical examination, repeat endoscopy, and imaging studies**

****LE may be considered in patients with good response or cCR following neoadjuvant therapy as assessed by physical examination, repeat endoscopy, and imaging studies, preferably in the setting of clinical trial**

*****Active surveillance may be considered patient with cCR following neoadjuvant therapy as assessed by physical examination, repeat endoscopy, and imaging studies preferably in the setting of clinical trial**

KEY: LAR = Low Anterior Resection; APR = Abdominoperineal Resection; LE = Local Excision; CRT = Chemoradiation

Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation