LOCAL EXCISION IN RECTAL CANCER

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Summary of Literature Review

Introduction/Background

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 and survival rates [2-4]. Postulating that early-stage lesions may not warrant such aggressive treatment as well as acknowledging the mortality and morbidity of these procedures, investigators have examined less morbid sphincter-sparing approaches such as local excision (LE). In addition, LE has been presented as an option to patients whose other comorbid conditions would not allow them to tolerate more extensive surgery. In recent years there has been additional evidence supporting the use of LE [5-9]. There has been growing interest in the use of neoadjuvant radiation therapy (RT) or chemoradiation therapy to improve outcome for patients with T1 or T2 cancers undergoing LE. The interest in the use of neoadjuvant RT or chemoradiation therapy is also in extending the indications for less radical surgery to selected patients with early-stage cancers at increased risk for local recurrence 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 LE RT or chemoradiation therapy in these patients [10-16].

Workup

All patients should receive a full colonoscopy with biopsy, pathology review, proctoscopy, carcinoembryonic antigen, and computerized tomography 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 [17], patients being considered for LE should have an endorectal ultrasound (EUS) 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 [18-20]. However, EUS may be more accurate for staging T1 and T3 rectal tumors and less accurate for T2 tumors [21], indicating the need for incorporation of other modalities in the workup of patients who are being considered for LE [22]. Magnetic resonance imaging (MRI) is more commonly included in the staging workup for patients with rectal cancer. High spatial resolution MRI of the pelvis provides more detailed anatomical information for locoregional staging, especially when the information to be gained may impact local treatment recommendations [23,24]. The prognostic value of preoperative high-resolution MRI assessment was evaluated in 374 patients with rectal cancer, demonstrating the superiority of MRI to AJCC TNM-based criteria in predicting risk of circumferential resection margin and assessing risk of LR, disease-free survival, and overall survival, as circumferential resection margin involvement is significantly associated with increased risk of distant metastatic disease [25].

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Surgical Techniques

There are 3 operative approaches for LE of a distal rectal lesion: transanal, posterior trans-sphincteric (York-Mason procedure), or posterior proctotomy (Kraske procedure). Transanal excision 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. The posterior trans-sphincteric and posterior proctotomy approaches are used less commonly and involve posterior approaches with dissection above or below the levator ani to the rectum [26]. 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. TEM has been shown to be as effective [27,28] and associated with less morbidity than conventional transanal excision [29,30] and is safe following chemoradiation therapy [29,31-36]. In fact, retrospective data suggest that LE or TEM used with or without neoadjuvant chemoradiation therapy in carefully selected patients staged with EUS and MRI demonstrate long-term control compared to data reported in the literature for patients treated with total mesorectal excision (TME) [37,38].

Patient Selection

Historically, the best candidates for LE include small (<4 cm), low-lying tumors confined to the muscularis propria (See Variant 1.). Patients with adverse pathologic features (mucinous/signet ring histology, poor differentiation, lymphovascular space invasion) or whose tumors occupy >40% of the rectum are at high risk for local recurrence, and LE is not recommended. These patients should be offered radical surgery [39,40]. Patients with positive margins after LE or piecemeal resections are at very high risk of local recurrence and should be offered immediate radical surgery. In general, patients with T2 tumors have a sufficiently high risk of lymph node involvement to warrant consideration of neoadjuvant 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 local recurrence 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. Radical surgery following chemoradiation therapy is considered standard of care for patients with T3 tumors able to undergo surgery, and neoadjuvant chemoradiation therapy followed by LE should be considered only in a clinical trial setting [12-16,41]. Palliative LE may otherwise be performed in advanced-stage patients [42].

Local Excision With or Without Radiation Therapy

Single-institution reviews have reported failure rates of 7%–40% and 25%–62% for LE alone in T1 and T2 tumors, respectively [5-9,32,33,35,43-51]. Postoperative RT may lower these rates to 10%–20% [5,9,11,40,43], and 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. Tumor diameter [52], pathologic T stage and extent of submucosal spread, high tumor grade, positive surgical margin, and perineural or lymphovascular invasion have been identified as independent predictors of recurrence following LE [14,53-56]. 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 [17].

In addition, patients with subclinical nodal metastases undergoing LE alone are at risk for recurrence. Female sex [57], age, upper tumor location, pathological features (high tumor grade, lymphovascular or perineural invasion, extensive submucosal spread), and deep invasion 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. However, restaging of patients being considered for LE following neoadjuvant therapy can be even more challenging using standard staging techniques. One prospective multicenter study demonstrated that restaging MRI using lymph node-specific contrast interpreted by an experienced radiologist can select rectal cancer with low risk of undetected nodal metastases (negative predictive value = 0.9) following neoadjuvant chemoradiation therapy and may be useful in identifying candidates for LE [58]. 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 pathologic complete response rate, which may identify patients who are candidates for LE following neoadjuvant chemoradiation therapy [59]. However, when considering LE following neoadjuvant chemoradiation therapy, evaluation of primary tumor response should be taken with caution as demonstrated in a retrospective study of 725 patients for which the incidence of lymph node metastases was 9.7% for ypT0 and 17.6% for ypT1 following neoadjuvant chemoradiation therapy and radical surgery [60].
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 chemoradiotherapy demonstrates promise in defining candidates for LE following neoadjuvant therapy [58].

An 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 chemoradiation therapy (54-65 Gy with 5-fluorouracil [5-FU] 1,000 mg/m² IV d1-3, d29-31) based on postexcision pathology [10]. Local recurrence rates were 7%, 8%, and 23% for T1, T2, and T3 tumors, respectively. 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 [11]. 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 overall survival rate was 85%, and the disease-free survival rate was 78% for all patients. Three of the 59 eligible T1 patients and seven of the 51 eligible T2 patients had experienced local failure. It is important to note, however, that these were highly selected patients and that one-third of patients were excluded after surgery due to large tumor size and/or questionable margin status (See Variant 3.).

More recently, LE or TEM following neoadjuvant radiation with or without chemotherapy has been reported. Data from retrospective studies [12,15,16,32,34,50,61] and two prospective studies [13,33] have demonstrated safety and local control rates ranging from 2.0%–13.2%. In one of these studies, a multi-institutional phase II trial was conducted by the American College of Surgeons Oncology Group (ACOSOG Z6041) investigating neoadjuvant chemoradiation therapy utilizing capecitabine and oxaliplatin followed by LE in T2 patients. Forty-four percent of patients achieved a pathologic complete response, 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. The therapy was associated with 39% of patients developing grade ≥3 treatment-related complications. The study demonstrated that chemoradiation therapy followed by LE for clinically staged T2N0 tumors results in a high pathologic complete response rate and negative resection margins but a high complication rate [13].

Simulation and Treatment Technique

Patients treated with 3-D conformal RT can 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) [62]. However, this position may be difficult for some patients to tolerate. 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) [63].

Alternatively, patients may be treated with intensity-modulated radiation therapy (IMRT) using a supine positioning. The dose-sculpting capabilities of IMRT reduce the need to displace bowel away from the treatment volume and potentially obviate the benefit derived from placing the patient in the prone position on a belly board. Retrospective comparison of 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) [63].

Hence, 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 frequent image guidance, as well as IMRT optimization using small-bowel dose constraints are also acceptable methods of treatment.

Future Directions

No studies to date have prospectively evaluated whether or not the use of neoadjuvant therapy reduces recurrence rates compared to LE or TEM alone. Future studies are designed to further evaluate the efficacy and safety of TEM following neoadjuvant chemoradiation therapy for rectal cancer patients at a higher risk for local recurrence. The CARTS-study (NCT01273051) is a multicenter feasibility study investigating the role of rectum-saving surgery for patients with clinical T1-3 distal rectal adenocarcinoma below 10 cm from the anal verge. In this study patients will receive neoadjuvant chemoradiation therapy (25 fractions of 2 Gy with concurrent capecitabine)
followed by TEM 8–10 weeks after the end of the preoperative therapy depending on the clinical response. The primary objective is to determine the number of patients with complete pathological response after chemoradiation therapy, and secondary endpoints will examine local recurrence rate and quality of life [41,65]. In addition, several other international trials will formally address the role of LE in rectal cancer. The French multicenter Groupe de Recherche Chirurgicale sur le Cancer du Rectum (GRECCAR) 2 trial (NCT00427375) will enroll patients with rectal tumors ≤4 cm to receive neoadjuvant chemoradiation therapy followed by reevaluation at 6–8 weeks. Patients with tumors ≤2 cm will then undergo either LE or TME [66,67]. A randomized Polish multicenter trial (NCT00738790) for patients with cT1-3, N0 rectal cancer will compare short course RT (5 × 5 Gy with a 4 Gy boost after 1 week) to standard fractionation chemoradiation therapy followed by LE performed 6 weeks after completion of neoadjuvant therapy [68]. Finally, the Spanish trial (NCT01308190) will randomize TME with chemoradiation therapy followed by LE in patients with clinically staged T2 or superficial T3 low rectal cancer [69]. We await the results of these randomized trials to help better define the role of LE following neoadjuvant therapy in selected patients.

Summary
- TEM is emerging as an option for LE and is associated with low morbidity rates compared to other techniques.
- LE alone may be an acceptable treatment strategy for uT1N0 rectal cancers without high-risk features associated with increased risk of recurrence
- Patients who undergo LE for early-stage rectal cancers and have known clinical or pathological adverse risk factors may benefit from adjuvant radiation or chemoradiation therapy.
- Patients with uT2N0 rectal cancers may be understaged by EUS and are associated with a higher risk of lymph node metastases. Adjuvant or neoadjuvant therapy should be considered in these patients.
- Although there are some single institution studies that suggest some uT3N0 rectal cancers may be treated with neoadjuvant chemoradiation followed by LE if a complete or near-complete tumor response is demonstrated on restaging studies, most of the patients who were included in these analyses were not surgical candidates. The standard of care for T3 lesions remains LAR or APR following neoadjuvant therapy, and the use of LE should be considered only in the setting of clinical trial or for those patients with severe comorbidities limiting surgery. We await the results of several randomized trials to better define the role of LE following neoadjuvant therapy for these higher risk patients.

Supporting Documents
- ACR Appropriateness Criteria® Overview
- Evidence Table

References


The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient’s condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.
Clinical Condition: Local Excision in Rectal Cancer

Variant 1: 57-year-old man with preoperative stage uT1N0 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 invasion is noted.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Excision, pT1N0 and Negative Margins</td>
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<td></td>
</tr>
<tr>
<td>Observation</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Local Excision, pT1N0 and Positive Margins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAR or APR</td>
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<tr>
<td>RT alone</td>
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<tr>
<td>Chemoradiation</td>
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<tr>
<td>Observation</td>
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</tr>
</tbody>
</table>

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

Discussion of Variant 1:
Patients with uT1N0 rectal cancers with negative margins and no clinical or histological factors associated with risk for local recurrence have excellent LC following LE alone. Risk factors associated with increased risk for local recurrence include tumor size >2.5 cm [52], adverse pathologic features (high-grade tumors and lymphovascular or perineural space invasion), or tumors occupying >40% of the rectum [14,39,40,53-56].
**Clinical Condition:** Local Excision in Rectal Cancer

**Variant 2:** 65-year-old otherwise healthy woman with preoperative stage uT2N0 moderately differentiated adenocarcinoma. Tumor is 3 cm in diameter, freely mobile, and is located 4 cm from anal verge. No lymphovascular space invasion is noted.

<table>
<thead>
<tr>
<th>Treatment Options</th>
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<tr>
<td>LAR or APR</td>
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</tr>
<tr>
<td>Local excision alone</td>
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<td></td>
</tr>
<tr>
<td>Local Excision followed by adjuvant chemoradiation</td>
<td>7</td>
<td>Depending on pathologic features of local excision, definitive surgery with LAR or APR may still be indicated.</td>
</tr>
<tr>
<td>Neoadjuvant chemoradiation followed by local excision</td>
<td>7</td>
<td>For this treatment, consider surgical management following neoadjuvant chemoradiation based on response to therapy.</td>
</tr>
<tr>
<td>Local excision and radiation alone</td>
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<td></td>
</tr>
</tbody>
</table>

**If Local Excision with Chemoradiation:**  
**Radiation Dose to Primary**

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>Rating</th>
<th>Comments</th>
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<tbody>
<tr>
<td>45 Gy/1.8 Gy</td>
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<td>This treatment is a preoperative dose. Infusional 5-FU or capecitabine should be used daily.</td>
</tr>
<tr>
<td>50.4 Gy/1.8 Gy</td>
<td>9</td>
<td>This treatment is a preoperative dose. Infusional 5-FU or capecitabine should be used daily.</td>
</tr>
<tr>
<td>54 Gy/1.8 Gy</td>
<td>7</td>
<td>This treatment is a postoperative dose. Infusional 5-FU or capecitabine should be used daily unless small bowel is in radiation field.</td>
</tr>
<tr>
<td>59.4 Gy/1.8 Gy</td>
<td>3</td>
<td>This treatment is a postoperative dose. Infusional 5-FU or capecitabine should be used daily unless small bowel is in radiation field.</td>
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**Simulation**

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<thead>
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<th>Simulation</th>
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<tr>
<td>Patient prone</td>
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<td></td>
</tr>
<tr>
<td>Small-bowel contrast at simulation</td>
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<td></td>
</tr>
<tr>
<td>Patient immobilized</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Use belly board</td>
<td>9</td>
<td>Consider this if the patient is prone.</td>
</tr>
<tr>
<td>Anal marker</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Bladder full at simulation</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Patient supine</td>
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<td>This is usually appropriate with IMRT.</td>
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**If Local Excision with Chemoradiation:**  
**Radiation Volume**

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<th>Radiation Volume</th>
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<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>L5/S1 to bottom of ischial tuberosity with GTV determined using CT/MRI based treatment to 2–3 cm below tumor</td>
<td>9</td>
<td></td>
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</table>

**Radiation Technique**

<table>
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<th>Radiation Technique</th>
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<th>Comments</th>
</tr>
</thead>
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<tr>
<td>IMRT</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3 field with photons</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>4 field with photons</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>AP/PA</td>
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</table>

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

ACR Appropriateness Criteria® 9   Local Excision in Rectal Cancer
Discussion of Variant 2:
Patients with uT2N0 rectal cancers may be less reliably staged with EUS [21], indicating a higher risk for subclinical nodal involvement and risk for recurrence. In addition, larger tumor size [52] may increase risk for local recurrence even if margins are uninvolved and no other adverse features are identified on final pathology. The addition of pelvic radiation with or without chemotherapy may reduce the risk of local recurrence [5,9,11,40,43]. Furthermore, neoadjuvant therapy should be considered for uT2N0 patients [13,55].

Clinical Condition: Local Excision in Rectal Cancer

Variant 3: 60-year-old woman with uT3Nx adenocarcinoma located 4 cm from anal verge.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Neoadjuvant chemoradiation followed by LAR or APR</td>
<td>9</td>
<td>See the ACR Appropriateness Criteria® “Resectable Rectal Cancer.”</td>
</tr>
<tr>
<td>Neoadjuvant chemoradiation followed by local excision</td>
<td>3</td>
<td>This treatment may be appropriate for patients who are not eligible for LAR or APR because of medical reasons.</td>
</tr>
<tr>
<td>Local excision alone</td>
<td>1</td>
<td></td>
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Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

Discussion of Variant 3:
Although there are some single-institution studies that suggest some uT3N0 rectal cancers may be treated with neoadjuvant chemoradiation followed by LE if a good tumor response is demonstrated on restaging studies, the standard of care for T3 lesions remains LAR or APR following neoadjuvant therapy, and the use of LE should be considered only in the setting of clinical trial or for those patients with severe comorbidities limiting surgery [12,37,58,59].