Controversies in Radiation for Upper Rectal Cancers

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Abstract
Over the past few decades substantial improvement has occurred in the diagnosis and treatment of rectal cancers. This disease requires the close cooperation of a multidisciplinary team, including radiologists, gastroenterologists, surgeons, medical oncologists, and radiation oncologists, to provide optimum treatment with minimal morbidity. The widespread use of total mesorectal excision (TME) and improvements in chemotherapy and radiation delivery have resulted in decreases in locoregional recurrence. Large randomized studies have shown a benefit with the use of preoperative chemoradiation for most patients with transmural and/or node-positive disease. Controversy remains, however, regarding whether this treatment paradigm should be applied uniformly to all patients regardless of tumor location. As the risk of local recurrence decreases with high rectal tumors and the benefit in terms of sphincter preservation is not applicable to this subgroup of patients, up-front surgery to allow for more accurate pathologic staging prior to making final treatment decisions is recommended. In patients with pathologically staged T3,N0,M0 tumors of the upper rectum who have undergone TME with 12 or more nodes removed, the addition of chemoradiation has very little benefit. (JNCCN 2012;10:1567–1572)

Accurate information regarding stage and location of the tumor is critical for treatment planning. The rectum is located in the pelvis, extending proximally from the rectosigmoid junction (where the tenia coli of the sigmoid colon splay to form the longitudinal muscle of the rectum) to the pelvic floor musculature that divides the rectum from the start of the anal canal. It measures approximately 12 to 15 cm in length, but varies depending on the borders used to determine the length as well as to individual anatomic variations. The rectum is divided into the lower, middle, and upper thirds, which are demarcated by the valves of Houston (Figure 1). The upper third of the rectum is covered with peritoneum anteriorly and posteriorly. The middle third has peritoneum only on a portion of its anterior aspect. The lower third of the rectum has no peritoneal covering. The 7th edition of the AJCC Cancer Staging Manual takes this into consideration and defines different T stages based on tumor invasion into either the surface of the visceral peritoneum or into surrounding structures. For example, tumors located in the mid or distal rectum that invade anteriorly will have direct invasion into other structures, such as the prostate, seminal vesicles, cervix, or vagina (T4b), whereas the same tumor located in the upper rectum is likely to only penetrate through the visceral peritoneum (T4a).1

Digital rectal examination can determine the distance of a low tumor from the anorectal ring/sphincter mechanism and may be sufficient to establish whether a sphincter-sparing operation may be performed. In patients with mid to upper rectal tumors, measurements of the distal edge of the tumor from the anal verge or dentate line are best determined endoscopically when the tumor cannot be reached by the examiner’s finger. The anatomy of the rectum and the relationship of the tumor to the valves of Houston are more important to determining the location of the tumor in the upper or mid rectum than is the measured endoscopic distance given the variability in the use of distal landmarks to determine this measurement. Because endoscopic measurements of distance to the tumor can be misleading, pelvic imaging with CT, MRI, and endorectal ultrasound (EUS) can help localize the tumor through the use of...
pelvic landmarks. These studies help determine the location of the tumor relative to the sphincter complex and other structures, such as the bladder, vagina/uterus, and prostate/seminal vesicles, and thus better clarify the tumor location relative to the peritoneal reflection.

All rectal cancers, regardless of level, should be staged appropriately to assess for distant metastases. Once a histologic diagnosis is established, a complete colonoscopy is performed to rule out synchronous primaries in the colon or rectum. If obstruction precludes this at initial evaluation, it should be performed before definitive surgery to determine the type of surgery required. If full endoscopic evaluation is not technically feasible before resection, then a completion colonoscopy should be performed within 6 months of resection. Pretreatment staging evaluation with CT scan of the chest, abdomen, and pelvis with oral and intravenous contrast is helpful to rule out metastatic disease to the lung and liver, the most common sites of distant metastases. Although PET scans are not routinely indicated, they can be considered in the evaluation of patients who present with symptoms or laboratory test abnormalities that increase the pretest probability of metastatic disease. They can also help localize disease for radiation treatment planning, especially in the setting of low rectal tumors, which are difficult to visualize on CT scans.

The treatment of rectal cancer is determined by the presence or absence of metastatic disease and the extent of local disease. Local staging of rectal cancers to assess depth of invasion (T stage) and nodal involvement (N stage) can be performed with pelvic MRI or EUS, with the choice often based on availability and institutional preferences. Several studies have indicated that the accuracy of T staging ranges from 80% to 95% for EUS versus 75% to 85% for MRI scans, whereas CT has shown a poorer accuracy of 65% to 70%. In a meta-analysis, the overall accuracy of detecting positive lymph nodes (LN) using any of these 3 modalities (MRI, CT, EUS) is only 50% to 75%. Because the enlarged LNs are not always metastatic (eg, reactive, especially after biopsies), the addition of fine-needle aspiration to EUS improves the ability to predict nodal stage but is subject to sampling bias.

Definitive surgical resection is the mainstay of treatment for rectal cancers. The primary objective is to achieve removal of the tumor with negative margins and to obtain adequate nodal staging. In most cases, a 2 cm distal surgical margin as well as a 2 mm or larger circumferential margin is needed. For low rectal tumors, a minimum of a 1 cm distal surgical margin is required. Total mesorectal excision (TME) is recommended, because this results in the lowest risk of local recurrence. The mesorectum is the fatty tissue that encompasses the rectum. Surgical excision, performed through sharp dissection in the plane between the fascia propria of the rectum and the presacral fascia, allows for en bloc removal of the primary tumor along with any tumor deposits within the mesorectum. Laparoscopic-assisted rectal cancer surgery is still undergoing clinical investigation, but many early studies have supported the safety and equivalent results of this approach versus an open technique. Ongoing studies are also evaluating the use of the robot as an adjunctive surgical tool in rectal cancer management.

For T1 cancers of the upper rectum, transanal endoscopic microsurgery may be an option in well-selected patients with favorable anatomy, but in general a more radical resection in the form of an anterior or low anterior resection (LAR) will be needed. Patients with pathologically staged T1 tumors undergoing limited surgical approaches may not need any postoperative therapy, especially if the tumor is located in the upper rectum. Patients with tumors that are T2 or greater have almost a 20% risk of LN involvement, and therefore would need chemoradiation if a local excision were performed. Even under these circum-

![Image](https://example.com/image.png)
stances, local recurrence rates are higher, and therefore a definitive surgical approach is preferred, such as an LAR (or abdominoperineal resection in select patients). All patients who elect not to undergo definitive surgery must be adequately counseled regarding their risks of recurrence and assessed for their ability and reliability to comply with a close follow-up plan.

The 1990 NCI Consensus Conference recommended adjuvant chemoradiation for all patients with wall-penetrating and/or node-positive disease. These studies, however, were performed before the widespread use of TME and the removal of 12 or more LNs. Although no prospective studies have evaluated the effect of distance from anal verge on the incidence of local recurrence, subset analyses of prospectively collected data from 27,8 of the 3 randomized trials suggested that, through univariate analysis, upper rectal tumors (defined as >10–11 cm) had lower local recurrence rates than middle or low rectal tumors. The Swedish Rectal Trial that used neoadjuvant short-course radiation resulted in a significant decrease in local recurrence for mid to low rectal tumors (P<.001 and P=.003, respectively), but no significant difference was seen in upper rectal tumors (P=.3; Table 1).10 Moreover, this was at a time before the widespread use of TME, and therefore higher rates of local recurrence would have been expected. In the Dutch TME trial, mid-rectal tumors and lower rectal tumors had a significantly higher risk of developing local recurrence compared with upper rectal tumors. Univariate subgroup analysis showed that patients with upper rectal tumors who received neoadjuvant radiation had no improvement in local recurrence rates (P=.17) compared with the surgery-alone cohort.11 These results were confirmed at 5-year follow-up (P=.122).7 Although these randomized studies did not evaluate the question of adjuvant chemoradiation for clinically staged T3,N0 cancers of the upper rectum, these subset analyses are consistent with each other and indicate a very low risk of local recurrence in upper rectal tumors that is not substantially reduced with the addition of neoadjuvant chemoradiation. Retrospective studies have shown that patients with T3,N0 cancers located in the upper rectum who have undergone TME and have at least 12 negative nodes have a very low risk of local recurrence (4%) and are unlikely to benefit from adjuvant radiotherapy.12 Several smaller retrospective studies have also found that patients with pathologically staged T3,N0 rectal cancer treated with surgery alone had very low recurrence rates and survival rates equivalent to those of patients treated with trimodality therapy.13-15

A study determining rates of pathologic complete response (pCR) and nodal involvement in 188 patients with clinically staged T3,N0 rectal cancers found that, despite being clinically node-negative, 22% had pathologically positive LNs after chemoradiation. Since preoperative chemoradiation results in sterilization of mesorectal LNs, the true incidence of upstaging is probably even higher.16 The authors, on the other hand, would argue that patients with clinically staged T3,N0 cancers of the upper rectum are better served with careful pathologic evaluation and selective treatment of only those who are at high risk of local recurrence, including those with close circumferential resection margins or who at time of surgery are found to have node-positive disease. A potential pitfall to the approach of surgery first is that patients who are upstaged at time of surgery will require postoperative chemoradiation. Randomized studies have established that preoperative chemoradiation is superior to postoperative chemoradiation therapy in terms of both short-term and long-term outcomes in patients.9 This needs to be balanced against the fact that the long-term bowel function of patients who are treated with surgery alone is superior to those who require radiation as a component of therapy.17

In patients with node-positive or T4 tumors of the upper rectum who need adjuvant chemoradiation, continuous-infusion 5-FU is used in conjunction with radiation. In a randomized study of 5-FU given either as bolus, as continuous infusion, or with semustine, continuous-infusion 5-FU was found to be superior, with an improved 4-year overall survival (OS) over bolus 5-FU (70% vs. 60%; P=.005).18 Therefore, 5-FU–based chemoradiation has become the current standard of care. A subsequent intergroup study (INT 0144) showed no difference in efficacy between bolus and continuous-infusion 5-FU, but did show a difference in toxicity, with greater myelosuppression in the bolus arms.19

In the early 1990s, studies began to use preoperative treatment for rectal cancer.8,10,20,21 Initially, preoperative radiation alone was used, consisting of 500 cGy in 5 fractions given 1 week before surgery. The subsequent operation in these studies was not
the currently used TME, and the surgery-alone arm had a local recurrence rate of 27%. Use of preoperative radiation not only resulted in a decrease in local recurrence to 12% but also led to an improvement in 13-year OS (58% vs. 48%; \( P = .004 \)).

Unfortunately, patients in the preoperative radiation-alone arm had increased toxicities with higher rates of small bowel obstruction (14% vs. 6%). The advent of TME resulted in fewer local recurrences, raising the question of the role of preoperative radiation in the setting of TME. Patients were randomized to preoperative short-course radiation using 500 cGy in 5 fractions followed 1 week later by TME versus TME alone. Long-term results show that radiation decreased 10-year local recurrence rates (11% vs. 5%; \( P < .0001 \)) without a difference in OS between the arms. As seen in Table 1, high rectal tumors in both the Dutch and Swedish trials had a lower local recurrence risk compared with middle and lower tumors. In both studies, short course preoperative radiation did not change local recurrence rates for high rectal tumors, but did significantly decrease local recurrence rates for middle tumors. It is unclear why the benefit of radiation for lower rectal tumors was only seen in the Swedish trial.

Neoadjuvant chemoradiotherapy has been shown to decrease local recurrence and improve pCR rates compared with radiation alone. In a randomized comparison of long-course chemoradiation (5040 cGy in 28 fractions with bolus 5-FU/leucovorin) versus preoperative short-course radiation (2500 cGy in 5 fractions), the long-course chemoradiation resulted in higher pCR rates (16% vs. 1%) and lower circumferential margin positivity (4% vs. 13%).

Table 1

<table>
<thead>
<tr>
<th>Location</th>
<th>Centimeters From Verge</th>
<th>Surgery Only</th>
<th>Preoperative Radiotherapy</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch Rectal Trial</td>
<td>High</td>
<td>&gt;10.1–15</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Middle</td>
<td>5.1–10</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>&lt;5</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Swedish Rectal Trial</td>
<td>High</td>
<td>&gt;11</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Middle</td>
<td>6–10</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>&lt;5</td>
<td>27%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Patterns of recurrence based on distance from anal verge.

\( *P < .01. \)
replace FU in adjuvant or neoadjuvant chemoradiation regimens.\textsuperscript{17} NSABP R-04 compared the use of capecitabine with continuous-infusion 5-FU (both with and without oxaliplatin), and both have been equivalent in terms of pCR, surgical downstaging, and sphincter preservation rates. Local recurrence and survival rates have not yet been reported.\textsuperscript{28} Two phase III European trials (STAR and ACCORD 12/0405-Prodige 2) evaluated the addition of oxaliplatin to 5-FU with radiation and found no difference in efficacy but significantly more toxicity in the oxaliplatin arms.\textsuperscript{29} Currently, chemoradiation with either continuous-infusion 5-FU or oral capecitabine remains the standard of care. No role exists for the addition of oxaliplatin to the chemoradiation regimen outside of a clinical trial.

Most commonly, the interval between completion of preoperative chemoradiation and surgery is 6 to 8 weeks. Retrospective studies have suggested that a longer interval is needed to achieve the maximal tumor response.\textsuperscript{30} Prospective phase II studies have confirmed this finding, showing higher pCR rates when the interval to surgery is increased.\textsuperscript{31} An ongoing study from the UK is comparing an interval of 8 to 12 weeks with that of 4 to 6 weeks (ClinicalTrials.gov identifier: NCT01037049).

\textbf{Conclusions}

With preoperative chemoradiation demonstrating superiority in terms of local recurrence and tolerability, most patients with rectal cancer are being treated using this approach. Despite improvements in imaging (CT, MRI, EUS, PET) the overall accuracy of nodal detection is only 50% to 75%. In the German Rectal Study, which randomized patients after pretreatment clinical staging to either preoperative or postoperative chemoradiation, 18% of patients who were clinical T3,N0 were found at time of surgery to be pT1 or pT2. All of these patients would have been overtreated.\textsuperscript{9} Despite the fact that clinicians are overtreating almost one-fifth of patients with rectal cancer, the preoperative approach is preferred for patients with mid to low rectal cancers because it is better tolerated and increases the chances of sphincter preservation. However, for patients with upper rectal cancers, the authors prefer avoiding radiation except for select patients with positive margins or concerning pathologic features.

\textbf{References}


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