The depth of post-treatment perirectal tissue invasion is a predictor of outcome in patients with clinical T3N1M0 rectal cancer treated with neoadjuvant chemoradiation followed by surgical resection

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KEYWORDS:
Rectal cancer; Neoadjuvant therapy; Rectal surgery

Abstract

BACKGROUND: To determine if patients with clinical stage III rectal cancer treated with neoadjuvant chemoradiotherapy (CRT) and surgery have an improved survival when the response to treatment results in a pathologic T3 tumor with a microscopic focus (≤5 mm) compared with a larger (>5 mm) invasion of the perirectal tissue.

METHODS: A retrospective review was conducted of 56 consecutive patients clinically diagnosed as T3N1M0 rectal cancer before treatment, who completed neoadjuvant CRT followed by surgical resection. Those with residual pathologic T3 disease (n=28) were analyzed separately. Clinicopathologic data including T stage, lymph node status, k-ras status, and differentiation were reviewed.

RESULTS: Among all 56 patients, there was no identified predictor of survival following neoadjuvant CRT and surgery. Among those with residual T3 disease, tumors extending >5 mm invasion into the perirectal tissue were associated with a higher risk of recurrence (50% vs 17%) and worse overall survival (4.3 vs 6.8 years, P=.015) when compared to tumors with ≤5 mm invasion into the perirectal tissue.

CONCLUSION: The depth of residual T3 tumor invasion into the perirectal tissue correlates with recurrence and overall survival in patients who underwent neoadjuvant therapy followed by surgical resection for clinically staged T3N1M0 rectal cancer.

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Patients with rectal cancer represent a subset of colorectal cancer patients who have been shown to have higher rates of recurrence after surgery alone due largely in part to its extraperitoneal location.1 Although surgery remains the cornerstone of therapy for patients with rectal cancer, a combined modality approach combining surgery, radiation, and chemotherapy (CMT) has been shown to reduce local recurrence.2 Within the past decades, multiple phase III
randomized trials, including the German CAO/ARO/AIO94 trial, have confirmed that preoperative chemoradiation is associated with significantly lower local failure and toxicity rates as well as an increase in sphincter preservation.3 Further studies have demonstrated that preoperative neoadjuvant chemoradiation may be associated with complete pathologic response, earlier tumor stage at the time of surgery, and significantly decreased number of positive lymph nodes and rate of metastasis.5 The accumulation of this data resulted in a shift from postoperative to preoperative chemoradiation as the standard of care.

However, although a considerable reduction in the local recurrence rates has been reported from these large trials, further improvement of survival rates is mainly limited to the prevention of death from distant metastasis. Although several studies have evaluated the effect of pathologic response, CEA levels, and distance from the anal verge on tumor downstaging as potential prognostic factors affecting survival, only circumferential resection margin has had a significant association with pathological response rate.6,7 Given the heterogeneity of this cohort, optimal treatment strategies for treated stage III rectal cancer remains largely unanswered.

For patients with stage III rectal cancer treated with neoadjuvant chemoradiotherapy and surgery, it is unclear whether patients with residual T3 tumor and a microscopic focus (<5 mm) invading the perirectal tissue have different survival outcomes than patients with residual T3 tumor and a larger (>5 mm) invasion of the perirectal tissue. The purpose of this study is to determine if the depth and pattern of invasion of residual tumor is a predictor of long-term outcome.

Methods

After internal review board approval, a retrospective review was conducted. From 1998 to 2008, consecutive patients who were initially referred for neoadjuvant chemoradiotherapy for clinically staged T3N1M0 rectal cancer were identified. Perioperative clinicopathologic data were collected and analyzed.

Patients were evaluated by a gastrointestinal multidisciplinary team. Preoperative clinical staging was on the basis of digital rectal examination, colonoscopy, endorectal ultrasound, computed tomography, or MRI of the chest, abdomen, and pelvis, and all tumors were identified in the lower two thirds of the rectum. All patients received preoperative chemoradiotherapy consisting of external beam radiotherapy with a total dose of 50.4 Gy and concomitant single agent 5-fluorouracil(FU)-based CMT. Following completion of therapy and restaging, patients underwent either sphincter-sparing surgical resection, when feasible, or abdominal perineal resection when the sphincter complex was involved with tumors as based on the patient’s initial presentation. All patients underwent total mesorectal excision and all patients were considered for adjuvant CMT.

Pathological evaluation

Pathologic staging was evaluated according to the AJCC 7th edition.9 All surgical specimens for this study were individually reevaluated by a single pathologist for depth and pattern of invasion as well as the extent of lymph node invasion. When residual T3 tumor was identified in the surgical specimen, the depth of invasion of the perirectal tissue was categorized into either ≤5 mm or >5 mm invasion. All tumor samples were then submitted for k-ras analysis.

Survival outcomes

Intention to treat strategy design was assigned for the population, which included adjuvant systemic therapy when deemed appropriate by the multidisciplinary gastro-intestinal team and treating medical oncologists. Long-term follow-up was accomplished by review of the medical chart and personal correspondence when adjuvant care was delivered outside of the institution. Patients presenting with recurrence of disease were classified as either local recurrence or metastatic. All patients were followed for at least 4 years or until death.

Statistical analysis

Descriptive statistics were calculated for all variables collected. Categorical variables were evaluated by the chi-square test. Continuous variables were assessed for normality and evaluated by Student t tests when normally distributed, and by Wilcoxon signed-rank test when not normally distributed. Survival was estimated by the Kaplan–Meier method and compared using the log-rank test. The level of statistical significance was set at P < .05. Statistical analysis was performed using SPSS version 14.0 (SPSS, Inc, Chicago, IL).

Results

During the time period 1998 to 2008, 62 patients presented with clinical T3N1M0 rectal cancer. The median age of the patients was 73 (range, 40–95), with a male to female ratio of 55% to 45%. Although 62 patients were included in the initial assessment, 6 patients were excluded from the study because of the findings of peritoneal and/or distant metastases at the time of surgery. Therefore, 56 patients were included in the study. Of these, 26 underwent an abdominal perineal resection and 30 underwent a low anterior resection. All patients had R0 resections. There were 2 deaths in the 30-day postoperative period. Table 1 represents the clinical, surgical, and pathological details of the patients.

Adjuvant CMT was administered to 35 of the 56 (65%) patients who underwent surgical resection. At a median follow-up of 58.5 months, 33/56 patients were alive (57%).
In total, 14 patients developed recurrent disease: 3 (5%) developed local recurrence and 11 (20%) developed evidence of distant metastases. For the 56 patients, there was no significant difference in recurrence or survival on the basis of all pathologic T stages, lymph node status, k-ras status, or differentiation.

We then analyzed the 28 patients who specifically had residual pathologic T3 disease. There was no difference in survival on the basis of k-ras or lymph node status or whether they received adjuvant CMT. This group was then separated on the basis of depth of invasion following resection and were defined as extending >5 mm invasion into the perirectal tissue (n = 6) or ≤5 mm (n = 22) invasion into the perirectal tissue (Table 1). Patients with >5 mm invasion had a higher recurrence after surgery than patients with ≤5 mm invasion into the perirectal tissue (50% vs 32%). Median overall survival was 6.8 years (95% CI 4.96–9.56) for those with ≤5 mm invasion compared with 4.3 years (95% CI 2.43–6.37) for those with >5 mm invasion. Overall survival (Fig. 1) is significantly different (P = .015) among groups with a 12-year survival of 17% vs 50%. In addition, patients with >5 mm perirectal invasion tended toward a worse 5-year disease-specific survival compared with those with ≤5 mm perirectal invasion (50% vs 77%, P = .08).

**Comments**

Neoadjuvant chemoradiation followed by surgery is the standard of care for stage III rectal cancer. The response to treatment has been shown to correlate with outcome. However, response is usually recorded as T and N stage.

![Figure 1](image)

**Figure 1** Overall survival on the basis of depth of subserosal invasion. This demonstrates the percentage of patients alive in years after their diagnosis on the basis of depth of invasion into the subserosa. All patients had surgical pathology staged as T3 by AJCC guidelines (n = 28). Patients with ≤5 mm subserosal invasion had an overall survival rate of 50%, 12 years after their diagnosis, whereas those with >5 mm invasion into the subserosa had an overall survival rate of 17%.

**Table 1** Overall survival on the basis of depth of invasion, adjuvant therapy, k-ras status, and lymph node status in patients with stage T3 rectal cancer

<table>
<thead>
<tr>
<th>Depth of subserosal invasion</th>
<th>N</th>
<th>Overall median survival (years) (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 mm</td>
<td>22</td>
<td>6.79 (4.96–9.56)</td>
<td>.015</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>6</td>
<td>4.32 (2.43–6.37)</td>
<td></td>
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<th>Adjuvant therapy</th>
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<tbody>
<tr>
<td>Received</td>
<td>16</td>
<td>5.89</td>
<td>.46</td>
</tr>
<tr>
<td>Did not receive</td>
<td>12</td>
<td>6.37 (1.50–8.04)</td>
<td></td>
</tr>
<tr>
<td>k-ras status</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wild-type</td>
<td>15</td>
<td>6.68 (3.88–9.10)</td>
<td>.89</td>
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<tr>
<td>Mutated</td>
<td>10</td>
<td>4.96</td>
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<table>
<thead>
<tr>
<th>Lymph node status</th>
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<tbody>
<tr>
<td>Negative lymph nodes</td>
<td>12</td>
<td>8.04 (3.87–9.56)</td>
<td>.16</td>
</tr>
<tr>
<td>Positive lymph nodes</td>
<td>16</td>
<td>5.89 (3.87–9.56)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.

*Not enough tissue for analysis in 3 patients.

T3 rectal cancer can be a spectrum of disease from microscopic to gross tumors. We evaluated outcomes on the basis of the actual pathologic depth of invasion into the perirectal tissue within the T3 staging. The decision to separate the groups on the basis of ≤5 mm invasion or >5 mm invasion was made because of a previous study suggesting that a 5 mm invasion is an independent predictor of survival in both colon and rectal cancers and should be used as a clinical pT subclassification.

The current data did not show any difference in outcomes for all patients undergoing treatment for T3N1M0 disease; however, in those with residual pathologic T3 disease, we did find a significant association with survival and depth of invasion with patients having ≤5 mm invasion demonstrating a longer median and 12-year survival. There were no other identifiable prognostic factors within this group that correlated with long-term outcome, including k-ras and lymph node status.

Most of the patients (65%) received adjuvant CMT. It is unclear from the records why patients did not receive adjuvant therapy as it was the standard of care at our institutions at that time. Regardless, there was no difference in survival between those patients who received adjuvant and those who did not. The actual CMT regimen is not available for review on each patient during the early period of the study, but in general, CMT recommendations changed over time. The early patients received 5-FU and Leucovorin, whereas the patients after 2003 received FOLFOX. On review, we did not find any survival difference on the basis of the year the patient was treated (data not shown). This study is not powered to show a significant difference on the basis of whether or not adjuvant CMT was used. All the patients received neoadjuvant 5-FU or Xeloda alone.

This study sample is small and retrospective and is therefore limited in the power to show significance in
survival; however, the fact that all patients were analyzed at least 4 years from the time of treatment gives strength to the survival data. This study demonstrates that the depth and size of tumor invasion into the perirectal tissue correlate with recurrence and overall survival in patients who underwent neoadjuvant therapy followed by surgical resection for what was originally clinically staged T3N1M0 rectal cancer and had residual T3 disease. Larger studies are warranted to determine if the depth of T3 invasion should be considered in the staging and prognosis of rectal cancer after neoadjuvant therapy and surgery.

References


Discussion

Ashwani Rajput (Albuquerque, NM): In your multidisciplinary group that treats the rectal cancer, how do you decide who gets the adjuvant therapy after the resections are performed? My second question to you has to do with the adjuvant therapies. Historically when we used just 5FU-based therapies, we used to quote about a 10% complete pathologic response for patients. Now in the era of multi-modality therapies with FOLFOX and FOLFIRI, we’re seeing actually 20% to 40% complete pathologic response rates. So I’m wondering, are you comfortable in your conclusions, just looking at the 5 millimeter metric or is it really the adjuvant therapies and maybe it’s the multi-modality 5FU group that are showing less than 5 millimeter. And so have you looked at your patients in terms of what other therapies they received?

Ms Brandt: All patients were considered for adjuvant therapy, and those that received adjuvant therapy were anyone that had node positive disease. Some patients that did not receive it just did not want to receive it or were too sick to receive it at the time. As to what therapies did we use with the 5FU and the complete response, all our patients had some sort of 5FU-based therapy, and we looked at FOLFOX and FOLFIRI and saw that there really wasn’t a difference.

Roderich Schwarz (Goshen, IN): I just have two brief questions for my own clarification. So only a small proximal portion of the rectum is actually serosalized, so when you say the term subserosal extension or invasion, are you just looking at proximal rectal cancers or are you looking at all? And you referred to subadventitial extension. Also, did you have a chance to look at the histopathologic response to preoperative therapies, so the extent of necrosis or perhaps the percentage of viable cells as an additional parameter that could actually be linked with subsequent outcomes?

Ms Brandt: I believe we were looking at all rectal cancers and just that depth of invasion into the subserosa, and if anything invaded into the subserosa, we would look at them no matter if they were proximal or distant. We didn’t look at pathologic response, so we will have to go back and take a look and see if that makes a difference, as well.

William C. Cirocco (Columbus, OH): Why 5 millimeters? We mostly go by T&M systems, as you pointed out. What was your sphincter preservation rate and how many coloanals did you do, and comment on circumferential margins.

Ms Brandt: We chose 5 millimeters due to a paper that was out a few years, but it wasn’t in rectal cancer specifically, and it wasn’t this specific group, so that’s why we evaluated it. I don’t have the data on sphincter-sparing surgery and coloanals or positive resection margins.