Midwest Surgical Association

Neoadjuvant therapy for rectal cancer decreases the number of lymph nodes harvested in operative specimens

Robert Amajoyi, M.D., Yoori Lee, M.D., Patrick J. Recio, D.O., Philip D. Kondylis, M.D.*

Department of Colorectal Surgery, c/o Colorectal Physicians & Surgeons of Pennsylvania, Saint Vincent, 145 West 23rd Street, Suite 201, Erie, PA 16502, USA

KEYWORDS:
Chemoradiation; Proctectomy; Lymph node; Rectal cancer; Specimen

Abstract

BACKGROUND: We evaluated the effect of neoadjuvant therapy (NAT) on lymph node harvest in rectal cancer patients undergoing anatomic resection with curative intent.

METHODS: A prospectively maintained database was retrospectively queried for rectal cancer cases from 1990 to 2010. Demographic data, NAT, and lymph node yield were analyzed. Nonanatomic resections were excluded.

RESULTS: Five hundred two cases were identified; the mean age was 68 years (range 34–89), and 56% were men. One hundred fifty-one (30%) patients received NAT. Overall, the lymph node yield was diminished in proctectomy specimens after NAT (mean = 9, median = 7) compared with specimens without therapy (mean = 13, median = 10, P = .001). Age was not a significant factor in the lymph node yield (P = .213 and .329). Among patients treated with NAT, younger patients had a significantly lower lymph node yield (P < .0001).

CONCLUSIONS: A decreased lymph node yield in proctectomy specimens from patients treated with NAT is consistent with prior studies. Younger patients had a greater reduction in lymph node harvest after NAT compared with senior patients.

© 2013 Elsevier Inc. All rights reserved.

Although surgical resection remains the primary treatment for rectal cancer, the use of neoadjuvant chemoradiation has increased. Its use is based on clinical trials that show it may improve local control and overall survival compared with postoperative adjuvant therapy.¹⁻² Nodal status is an important prognostic factor in the management of rectal cancer. The actual number of lymph nodes retrieved is very variable. From the recommendations of the American Joint Committee on Cancer and the International Union Against Cancer (IUAC), the number of lymph nodes harvested from the specimen required for the adequacy of resection is set at 12 lymph nodes. Since then, this has been the recommendation.³ A diminished proctectomy lymph node yield has been reported in the setting of neoadjuvant chemoradiation for rectal cancer. We evaluated the effect of neoadjuvant therapy (NAT) on lymph node harvest in rectal cancer patients undergoing anatomic resection.

Methods

Patient selection

After approval from the Institutional Review Boards at both Saint Vincent Health Center and University of...
Pittsburgh Medical Center-Hamot, data from a prospectively maintained database from the Regional Cancer Center (RCC), Erie, PA, was retrospectively queried for total and partial mesorectal excision of rectal cancer cases from 1990 to 2010. The Regional Cancer Center has a catchment population of approximately 800,000. It covers a territory including Northwest Pennsylvania, North Central Pennsylvania, and portions of both Western New York and Eastern Ohio. Patients were excluded if they had previous local excision, prior proctectomy, and a history of previous pelvic irradiation. Patients with metastatic disease were not excluded. Patients over the age of 65 years were defined as more senior. Cancers contained within 5 cm of the dentate line were defined as lower third rectal cancers. Those within 6 to 10 cm of the dentate line were defined as middle third rectal cancers. Those within 10 to 15 cm from the dentate were defined as upper third rectal cancers. Those within 5 cm of the dentate line were defined as middle third rectal cancers. Those within 10 to 15 cm from the dentate were defined as upper third rectal cancers. Age, sex, stage, NAT, and lymph node yield were analyzed.

Treatment

The neoadjuvant radiation treatment regimen was 45 Gy in 25 fractions over 5 weeks with synchronous 5-fluorouracil in the 1st and 5th weeks of radiation.

Surgery

All cases were performed by fellowship-trained colorectal surgeons who uniformly used techniques of either total or partial Total Mesorectal Excision (TME). The 10 contributing surgeons were faculty within an Accreditation Council for Graduate Medical Education–accredited colorectal surgery training program.

Pathology

Fat-clearing techniques for lymph node identification were performed by request only since the mid-1990s and became standard in 2005. Hematoxylin-eosin staining was used for the identification of involved lymph nodes. Neither bread loafing nor immunohistochemistry node assessment was routinely used.

Statistical analysis

Statistical analysis was performed using SPSS version 10 (SPSS Inc, Chicago, IL). The Mann-Whitney U test was used for numeric data. Results were expressed as both the mean and median. A P value <.05 was considered significant.

Results

Five hundred two cases were identified for analysis; 56% were male and 44% were female patients. The mean age of the subjects was 68 years (range 34–89 years). Low anterior resection accounted for 72% of cases. Abdominoperineal resection was performed in 24%. Handsewn coloanal reconstruction was performed in 4%. The open surgical technique was used in 97% of cases. Pathologic tumor staging identified 21% T1, 23% T2, 50% T3, and 6% T4 tumors. Pathologic nodal staging identified 22% N1 and 11% N2.

Total Mesorectal Excision (TME) was used for abdominoperineal resection. All other cases used partial mesorectal excision with truncation of the mesorectum when an adequate distal margin was identified. The cancer was contained entirely within either the lower or middle third of the rectum in 71% (n = 358); 29% were upper third rectal cancers (n = 144). One hundred fifty-one (30%) patients received NAT. There was no significant difference in proctectomy lymph node yield between the selective and routine mesenteric fat-clearing eras.

Overall, the mean lymph node yield for proctectomy specimens without NAT was 13, with a median of 10 lymph nodes. In contrast, specimens after NAT had a mean lymph node yield of 9, with a median of 7 lymph nodes. The difference between the 2 groups was significant (P = .001). For partial and total proctectomy, the lymph node yield was consistently less with NAT than their non-NAT cohort.

We found that the percentage of adequate lymph node yield among the total proctectomy patients was lower in the NAT group. The same subgroup analysis was performed for the partial proctectomy group. The partial proctectomy neoadjuvant group also had a lower percentage of adequate lymph node harvest. Of the 151 patients with NAT, 142 were limited to the lower and/or middle third of the rectum, and more of these specimens yielded at least 12 nodes. The percentage of patients with at least 12 nodes in the non-NAT group was 72%.

Rectal tumor height

On subgroup analysis, upper third cancer specimens yielded statistically more lymph nodes than lower/middle third rectal cancer specimens (mean 14 vs 11, median 12 vs 9; P < .0001). Furthermore, NAT was associated with a decreased lymph node yield (mean 12 vs 9, median 10 vs 7; P = .022) in lower/middle third rectal cancer but did not affect the lymph node yield in cancers that involved the upper third of the rectum (P = .869). However, only 9 of these upper rectal cancer patients (6%) received NAT.

Age

Neoadjuvant treatment was administered to a greater proportion of younger patients (ie, ≤65 years) with rectal cancer (n = 65, 36%) than older patients (n = 86, 27%). Age alone was not a significant factor in the lymph node yield (P = .329). Younger patients (ie, ≤65 years) with NAT had a significantly decreased lymph node yield relative to non-neoadjuvant patients (mean 9 vs 14, median 7
vs 11; \( P < .0001 \)). In older patients, the lymph node yield was not statistically significantly different with NAT \( (P = .172; \text{mean 12 vs 10, median 10 vs 8; Table 1}) \).

**Comments**

Neoadjuvant chemoradiation has been associated with a decrease in pathologic stage for both tumor and nodal status in about 60% of those treated and a pathologic complete response in 8% to 31% of patients.\(^4\) Our study is consistent with previous findings that NAT significantly decreases the lymph node yield from proctectomy specimens.

Age alone was not a factor in the overall lymph node yield. Among patients receiving NAT, a significantly decreased lymph node yield was found in younger patients but not in older patients (ie, >65 years). Further investigation would be warranted to determine if this result translates to a greater response to NAT by younger patients and whether this impacts recurrence and survival. Because of the database structure, we were not permitted to evaluate the impact of body mass index or an individual pathologist. The results from our study reinforce those of previous authors indicating that NAT leads to a significantly lower proctectomy lymph node yield.\(^1\,\(^2\)\)

Habr-Gama et al\(^10\) suggested that this may reflect the response to NAT rather than a suboptimal oncologic technique or pathologic examination. It is now established that not all specimens will meet the 12 lymph node marker in patients with NAT. It is evident that the finding of fewer lymph nodes retrieved after NAT is not uniformly caused by the use of a suboptimal technique by the surgeon or pathologist. Marks et al\(^11\) showed that the number of lymph nodes harvested after NAT varied greatly even when the surgery and pathologic evaluation were standardized. In the same study, there was no statistically significant difference in regard to the type of surgery. There was also no significant difference in the number of lymph nodes harvested based on the individual pathologist. The results from our study reinforce those of previous authors indicating that NAT leads to a significantly lower proctectomy lymph node yield.\(^1\,\(^2\)\)

Currently, there is still no consensus on the interpretation of a low lymph node yield after NAT. It is unclear how having fewer nodes available for interpretation impacts prognosis. Therefore, the use of lymph node harvest as a quality measure of surgical technique for rectal cancer warrants reevaluation. This is relevant because we found significantly fewer nodes in both partial and total proctectomy patients with neoadjuvant treatment. Additionally, mid- and lower rectal cancers had fewer nodes identified than upper rectal cancers.

**References**

6. Kim YW, Kim NK, Min BS. The influence of the number of retrieved lymph nodes on staging and survival in patients with stage II and III

<table>
<thead>
<tr>
<th>Age</th>
<th>Therapy</th>
<th>LN count (mean ± SD)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 y (n = 182)</td>
<td>+ NAT = 65</td>
<td>8.6 ± 7.64</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>− NAT = 117</td>
<td>14.5 ± 12.41</td>
<td></td>
</tr>
<tr>
<td>&gt;65 y (n = 320)</td>
<td>+ NAT = 86</td>
<td>12.0 ± 10.94</td>
<td>.172</td>
</tr>
<tr>
<td></td>
<td>− NAT = 234</td>
<td>9.8 ± 8.51</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

William C. Cirocco, M.D. (Grosse Pointe Woods, MI): The authors nicely present 20 years of data on the presence of lymph nodes in rectums removed for carcinoma in an era of increasing use of NAT for rectal cancer and also an era of magnified focus on lymph node harvest in colorectal cancer since the selection of 12 as a standard. In this study, the authors use age 65 as the break point of young vs old with almost two thirds of young patients undergoing neoadjuvant therapy vs only 27% in the older population. I believe this 2- to 3-fold increased use of NAT may explain the lower number of lymph nodes harvested in young rectal cancer patients vs older patients, which goes against the current understanding that increasing age correlates with decreasing numbers of lymph nodes. Were you able to break out your low anterior vs Abdominoperineal Resection (APR) specimens? I would expect more nodes with APR and completely resected rectums with their lymph bearing mesentery. Why include rectal sigmoid cancers? Do you recommend neoadjuvant cancer for this subgroup of patients? Third, you had 3 subgroups of patients with less than 6 nodes, 6 to 12 nodes, and greater than 12 nodes. Although 12 nodes may not be possible for many of these patients, are you suggesting that 6 perhaps should be an acceptable number or perhaps a new standard? Should we have a target number of lymph nodes for all rectal cancer especially after NAT? Can this truly be a surrogate for an oncologically sound rectal resection? Finally, you note that survival is not influenced by the number of nodes obtained, but do you have survival data to support this claim?

Robert Amajoyi, M.D. (Erie, PA): Regarding the first question (ie, low anterior vs APR specimens), we did not distinguish between the 2. They both were lumped into 1 category. There was no way to differentiate between the 2, so we looked at the prospective data; that information was not given to us. For the second question regarding why we included rectal sigmoid cancers, these were upper rectal cancers that extended into the sigmoid and the rectal sigmoid junction, so we included them as upper rectal cancer. In response to your third question, less than 6 lymph nodes is not enough. It is not acceptable. I mean after NAT we do expect complete responders, which are patients who have 0 lymph nodes found. You can expect no lymph nodes—I mean, negative lymph nodes completely. You can also expect some positive lymph nodes and negative lymph nodes. Therefore, the target of 12 lymph nodes is unrealistic. In John Mark’s study in 2008, Diseases of the Colon & Rectum (DCR), including 176 patients after NAT, greater than 72% of his patients had lymph nodes and 32% had less than 6 lymph nodes. Therefore, the question is after NAT is that number really a realistic number? As you can tell, if you have complete responders, then we have to question whether that number is realistic.

Philip D. Kondylis, M.D. (Erie, PA): If I could clarify the first question and answer, we did specifically look at abdominoperineal resection vs rectal cancer in the lowest third, and they were indistinguishable. Therefore, we pooled them together for the remainder of the analysis.