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Neoadjuvant Therapy and Local Excision of Rectal Adenocarcinoma

Thomas E. Read, MD, FACS, FASCRS

Disease-free survival and local pelvic control after local excision alone for rectal adenocarcinoma are not as good as after proctectomy. If local excision is to be offered to select patients with distal rectal cancer as curative therapy, neoadjuvant chemoradiation may improve outcome. Neoadjuvant therapy may downsize and downstage the tumor and sterilize the margins of resection. In addition, recent data suggest that mesorectal nodal status can be predicted by histologic T stage following neoadjuvant therapy, leading to more accurate selection of patients for expectant follow-up after local excision versus proctectomy. Patients who have an excellent clinical response to neoadjuvant therapy may be initially offered local excision. If pathologic analysis reveals ypT0-1 disease, the risk of nodal metastases is approximately 3%. Proctectomy can be reserved for patients proven to have residual ypT2-4 disease. Before widespread adoption, it will be critical to prospectively compare results of this treatment algorithm with proctectomy.

KEYWORDS neoadjuvant therapy, local excision, rectal cancer

Standard therapy for adenocarcinoma of the distal rectum has been proctectomy, either by abdominoperineal resection or by low anterior resection. However, proctectomy is associated with substantial perioperative morbidity, anorectal functional derangements, and, in the case of abdominoperineal resection, permanent fecal diversion.[1,2] In an attempt to minimize morbidity and preserve the anal sphincter, some authors have advocated local excision as an alternative approach for select patients with small distal rectal tumors.[3-9] Although initial results of local excision appeared promising, long-term outcome analysis has revealed that disease-free survival and local pelvic control are not as good as after proctectomy.[10-13]

Large studies of local excision for early-stage rectal cancer have reported disease-free survival rates of less than 80% and suboptimal local pelvic control rates.[7,12] The Cancer and Leukemia group B (CALGB) series authored by Steele and coworkers reported disease-free survival of 78%, with patients with T2 tumors treated with postoperative chemoradiotherapy. Local pelvic failure was reported in 10 of 110 patients (actuarial analysis was not provided). The University of Minnesota group reported disease-free survival of 79% for T1 tumors and 53% for T2 tumors, without the use of adjuvant radiotherapy.[12] Local pelvic control was only 72% overall, 82% for T1 tumors and 53% for T2 tumors. Although these results have been used by some authors as an argument *for* local excision as definitive therapy for patients with distal rectal cancers, they compare poorly to results after proctectomy.[11-16] The University of Minnesota group reported disease-free survival of 91% for T1N0 tumors and 84% for T2N0 tumors, and local control of 96% for T1-2N0 tumors, all treated by proctectomy alone.[12]

Although some smaller studies have reported better results after local excision, evaluating the results of many of these trials is difficult because of methodological problems. Some authors exclude patients with positive margins of resection from analysis, instead of including them on an intention-to-treat basis, biasing the results toward the success of local excision. Many fail to perform actuarial analysis when reporting disease-free survival and local pelvic control, instead reporting crude fractions, which again biases the results toward the success of local excision. Due to the small numbers of patients with early-stage distal rectal adenocarcinoma, most of the trials have small numbers of patients and may be of inadequate power to adequately test their hypotheses. Virtually none report 95% confidence intervals in their survival analyses.

From the Division of Colon and Rectal Surgery, Colon and Rectal Surgery Residency, Western Pennsylvania Hospital, Clinical Campus of Temple University School of Medicine, Pittsburgh, PA.
Address reprint requests to: Thomas E. Read, MD, Dept. of Surgery 4600N, Western Pennsylvania Hospital, 4800 Friendship Ave., Pittsburgh, PA 15224. E-mail: tread@wpahs.org.

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One of the purported advantages of local excision in the treatment of patients with rectal adenocarcinoma is that if tumor recurs in the pelvis, the patient can be salvaged by performing proctectomy when recurrence is detected. This argument fails for the following reasons. Pelvic recurrence may be due to implantation of viable tumor in extrarectal tissue at the time of local excision or progression of occult mesorectal nodal disease. In both scenarios, there is often a substantial time lag before such disease is detected because of symptoms, intraluminal extension, or radiographic detection. This time lag may allow for metastatic spread or pelvic side-wall invasion, which would preclude cure. The number of patients reported in the literature undergoing salvage proctectomy after failed local excision is small, and the problems with methodology noted in the above paragraph are magnified when evaluating results of therapy for a very small number of patients. In practice, salvage proctectomy after local pelvic failure does not provide results equivalent to proctectomy as initial treatment.[17]

There is thus serious concern regarding the use of local excision as definitive treatment for otherwise healthy patients with distal rectal adenocarcinoma. Local excision is most often employed in patients with early-stage tumors, those that are readily cured by proctectomy. To jeopardize this cure in an attempt to preserve the anal sphincter musculature may reflect poor judgment. One strategy to improve oncologic outcomes in patients undergoing local excision is to utilize neoadjuvant radiotherapy, which has been shown to improve outcomes when combined with proctectomy for rectal cancer.[16,18]

Neoadjuvant Radiotherapy and Local Excision

Neoadjuvant radiotherapy or chemoradiotherapy may improve outcomes by downsizing and downstaging the tumor and sterilizing the margins of resection. Given the technical challenges of local excision and the relatively high number of patients with positive margins of resection,[7] this effect cannot be underestimated. In addition, neoadjuvant therapy may sterilize intraluminal tumor and prevent viable tumor cells shed during local excision from implanting in extrarectal tissue. In addition, recent data suggest that mesorectal nodal status can be predicted by histologic T stage following neoadjuvant therapy, leading to more accurate selection of patients for expectant follow-up after local excision versus proctectomy.[19]

Predicting Mesorectal Nodal Status

Local excision can only cure tumors confined to the rectal wall; thus patient selection is critical to the success of treatment. One of the great uncertainties during local treatment of rectal cancer is the status of mesorectal lymph nodes. Although transrectal ultrasound (TRUS), computed tomography, and magnetic resonance imaging have all been utilized to assess mesorectal lymphadenopathy, none of the techniques can accurately determine the presence or absence of nodal metastases.[20,21]

However, it is possible to estimate the rate of nodal metastases by examining mural tumor burden. The risk for tumor spread to mesorectal nodes after proctectomy in the absence of neoadjuvant therapy is reported to be 0 to 13% for T1 tumors, 12 to 28% for T2 tumors, and 36 to 79% for T3/T4 tumors.[22-26] Unfortunately, these rates have substantial variability and overlap each other. If patients with T1 tumors knew that they had a possible 1 in 8 chance of mesorectal nodal metastases, would they ever agree to be treated with local excision alone?

Some investigators have utilized neoadjuvant radiotherapy or chemoradiotherapy combined with local excision in small series of select patients,[27-30] and some have based their decision to proceed with immediate proctectomy on the pathologic T stage (ypT) of the excised lesion.[28] However, other authors have noted that ypT stage after neoadjuvant chemoradiotherapy may not be predictive of nodal status, calling this practice into question.[31] Our group has recently evaluated the relationship between histologic T and N stages following neoadjuvant radiotherapy or chemoradiotherapy and proctectomy in a large series of patients and found that histologic stage of the remaining mural tumor correlated with nodal status.[19] Of 644 patients undergoing neoadjuvant therapy and proctectomy, lymph nodes harboring metastatic tumor were found in 1/42 (2%) of ypT0 patients, 2/45 (4%) of ypT1 patients, 43/186 (23%) of ypT2 patients, 158/338 (47%) of ypT3 patients, and 16/33 (48%) of ypT4 patients ($P < 0.0001$, Chi-squared). Overall, there appeared to be a sharp increase in the rate of nodal metastases between ypT1 and ypT2 tumors; therefore, we grouped the patients as ypT0-1 and ypT2-4. The probability of finding ypN+ disease was 3% in patients with ypT0-1 residual primary tumors versus 39% in patients with ypT2-4 residual primary tumors ($P < 0.0001$, Fisher's exact test). Complete histologic response (no residual mural or nodal disease) was more common after chemoradiotherapy (11%) than after short-course radiotherapy (5%) or long-course radiotherapy (3%) ($P < 0.002$, Chi-squared).

Our data indicate that nodal metastases are rare in patients whose mural tumor burden shrinks to ypT0-1 following neoadjuvant radiotherapy or chemoradiotherapy. The striking difference in nodal metastasis rates between patients with ypT0-1 tumors and those with ypT2-4 tumors following neoadjuvant treatment may reflect the differential response of some tumors to neoadjuvant treatment,[32] or to the pretreatment stage of the lesion.[33] Regardless, long-term oncologic results following neoadjuvant radiotherapy and proctectomy appear to be more related to the final histologic stage of the tumor rather than to pretreatment estimates of tumor stage.[14-16,18,29,34]

Surgical Therapy Based on Mural Tumor Response to Neoadjuvant Therapy

As some investigators have reported, it is feasible to perform local excision of distal rectal tumors that have an excellent