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Predicting the risk of lymph node metastasis in early rectal cancer

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A B S T R A C T

As surgery for rectal cancer progresses to less invasive approaches, there is increasing interest in local excision techniques. Paired with this is the progress of surgical techniques to achieve local excision. From traditional transanal excision techniques, we have progressed to transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TAMIS), and potentially transanal radical resection. The Achilles' heel of local excision for rectal cancer is the inability to assess lymph node status in the mesorectum. If lymph nodes containing cancer are left behind following local excision, persistent and recurrent disease is inevitable. To date, we do not have a completely reliable method to assess these lymph nodes aside from radical resection. In this article, the authors review the current means to evaluate lymph node status in rectal cancer with histopathologic characteristics and various imaging techniques. Although these modalities have some merit, their assessment of lymph node involvement in rectal cancer is incorrect in 20% or more of instances, making it difficult for a surgeon to base critical oncologic decisions on them. Hopefully, further technological advances can improve accuracy in this field and expand the possibility for local excision in rectal cancer in the future.

Progress in the field of surgery includes increasing successful results while minimizing morbidity to the patient. Perhaps one of the clearest examples of this fight to decrease morbidity and improve quality of life for the patient is in the resection of rectal cancer. The pelvic dissection in a low anterior resection or abdominoperineal resection carries with it significant morbidity and mortality including the potential for bowel and bladder dysfunction, stool clustering, incontinence as well as sexual dysfunction. While advances in minimally invasive surgery have significantly reduced the morbidity of these procedures, they nonetheless remain.

In an effort to decrease morbidity or in the treatment of medically frail patients, local treatment of rectal cancer has for decades been an option for management of the disease. Because early results of low anterior resection and abdominoperineal resection carried with it a substantial rate of local recurrence, perhaps at one time accepting higher local recurrence rates for early rectal cancer treated by local excision alone was justifiable. However, with increasing focus on improved surgical technique with TME and the use of neoadjuvant therapies, there has been a significant reduction in local recurrence rates following radical surgical resection of rectal cancer at all stages.

Although local excision of rectal cancer removes the primary tumor, it does not address the tubular lymphatics and lymph nodes that are the predominant gateways of metastatic disease. Although recurrence of rectal cancer can be due to margin status or intraluminal drop-metastasis, persistent disease from unaddressed lymph nodes remains the major concern when considering local excision. Were we to be fully convinced that the tumor in question was confined to the primary site, local excision has a dramatic upside compared with the alternative surgical options. Aside from the aforementioned potential morbidities, most importantly abdominal surgery may include permanent colostomy as the end result. Without being convinced of the nodal status of the primary tumor, local excision of an invasive rectal cancer (particularly local excision without neoadjuvant therapy) carries with it substantially increased risk of local recurrence when compared with radical resection.

The key, then, is to predict the risk of lymph node metastasis as accurately as possible. If this could be done, then local excision for those with low risk for positive lymph nodes could safely undergo local excision with acceptable rates of local recurrence. This would avoid the morbidities of radical resection. The purpose of this article is to review the data available, including histopathologic considerations and imaging characteristics, to assess the risk of lymph node metastasis in rectal cancer and offer the clinical implications of these findings.

Histopathology of the tumor

In clinical practice, treatment decisions follow the initial diagnosis of rectal cancer. Many of these are based on the stage

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of the disease. There has been considerable research into which histopathologic features of the primary tumor indicate high risk for lymph node metastasis. This analysis is based on histological analysis of either endoscopic biopsies or transanal excision of the primary tumor. A local excision can be either diagnostic or therapeutic, depending on the tumor stage. A full-thickness excision of the cancer, using either standard instrumentation or more advanced transanal endoscopic surgery (TES) technologies such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS) allows for a complete excision of the cancer without fragmentation or compromise of the cephalad tumor margin, which is often at risk with a transanal approach. This large specimen allows for the fullest examination of the cancer and a definitive assessment of the T stage. If there were highly predictive accurate characteristics of the primary tumor that indicated lymph node metastasis, one could consider local excision as definitive therapy.

Many histological tumor characteristics have been analyzed throughout the literature to determine their predictive significance for lymph node disease. These include tumor differentiation, visible lymphatic or vascular invasion, perineural invasion, and tumor budding. In addition, overall tumor size and level of tumor from the anorectal ring have been indicated as potential risk factors, with some authors indicating that larger and lower tumors suggest increased risk of lymph node metastasis. However, to date, the T stage, with further subdivisions of submucosal (sm) invasion (i.e., sm 1, 2, or 3) beyond the standard T stage definition, remains the most useful predictor of nodal involvement.

Depth of invasion, tumor size, and location in the rectum

Tumor size alone is not a risk factor for lymph node metastasis. Although some have postulated that a tumor >3 cm involving $>40\%$ of the rectal circumference may be an indicator of high risk for positive lymph nodes, studies do not prove this to be the case. Blumberg et al.[1] studied 3318 patients with T1 or T2 cancers comparing tumors for size greater or lower than 3 cm and found no significant difference in lymph node metastasis ($p = 0.77$). While the size alone may not be an indicator of positive lymph nodes, certainly the technical challenge of excising a cancer greater than 3 or 4 cm can lead to a higher local recurrence rates. This may not be due to regional lymphatic spread but rather from incomplete excision of the primary tumor.[2] The rates of this type of local recurrence can be lessened with TES excision as opposed to traditional transanal excision.[3]

The level of the cancer in the rectum has been shown to correlate to risk of lymph node metastasis, with lower tumors spreading to lymph nodes more often. Nascimbeni et al. looked at 353 patients with T1 tumors. Among tumors in the lower third of the rectum, 34% had lymph node metastasis.[4] Tumors in the mid and upper third of the rectum had lower rates of metastasis, with 11% and 8%, respectively. A multivariate analysis was performed confirming this finding ($p = 0.007$).

While it is clear that the rate of lymph node metastasis is greater for T2 than T1 cancers, subanalysis into the depth of T1 and T2 penetration correlates with nodal spread. T1 cancers have been broken down into sm 1, sm 2, and sm 3 levels, defined as upper third, middle third, and lower third of the rectal submucosa, respectively. In the aforementioned article by Nascimbeni et al.,[4] sm 3 tumors had a 23% incidence of nodal disease, while sm 2 and sm 1 rates of nodal disease were 8% and 3%, respectively. These findings have been echoed in T2 cancers as well. Salinas et al.[5] showed T1 sm 3 or T2 levels of invasion to be the only predictor of lymph node metastasis on logistic regression analysis.

The level of submucosal invasion as a predictor of lymph node disease was refuted by Rasheed et al.[6] who evaluated T1 and T2 tumors for lymph node involvement. They did not find that the depth of submucosal invasion affected lymph node status, although the numbers in their study were substantially smaller, with only 55 patients in the T1 group.

Ding et al.[7] found a similar correlation of nodal involvement with depth of invasion specific to T2 cancers. Depth of invasion into the muscularis propria was an independent predictor of lymph node metastasis. T2 tumors were divided into invasion of inner circular muscle layer (superficial) and invasion of outer longitudinal muscle layer (deep). Risk of lymph node metastasis was 15.3% for superficial T2 tumors vs. 27.6% for deeper T2 tumors. This was found to be significant on multivariate analysis ($p = 0.033$).

Differentiation and lymphovascular invasion

Both poor differentiation of tumor cells and visible lymphovascular invasion have been shown to indicate high risk of lymph node metastasis. Chang et al.[8] studied 943 patients with T1 and T2 rectal cancers. Lymph node metastasis was found in 19.9% of all patients. On multivariate analysis, lymphovascular invasion, poor differentiation, and depth of invasion (i.e., T2) were significantly related to lymph node involvement. There were 11.7% and 23.1% of patients with T1 and T2 cancers with lymph node metastases, respectively ($p = 0.032$). Lymphovascular invasion and poor differentiation were significant variables on multivariate logistic regression analysis with an odds ratio of 11.472 (95% CI: 7.198–18.284; $p < 0.001$) and 3.218 (95% CI: 1.377–7.519; $p = 0.007$), respectively.

Perineural invasion and tumor budding

Perineural invasion has been suggested as a risk factor for lymph node spread as well, though less well supported in the literature. Saclarides et al.[9] found that perineural invasion significantly influenced nodal disease among 62 radically excised rectal cancers. They found this variable to have sensitivity and specificity of 46% and 88%, respectively ($p = 0.029$), with a resulting high positive predictive value of 86%.

Tumor budding is another suggested indicator of lymphatic spread. Tumor budding is described by Ueno et al.[10] as clusters of up to 4 cells in the invasive front of the invasive cancer. The presence of more than 10 buddings viewed in a 200-fold magnification is considered positive. Okuyama et al.[11] looked at budding as a risk factor for lymph node metastasis and found that including budding with lymphovascular invasion indicates increased risk of lymph node metastasis.

Although all of the above are indicators of increased risk of nodal disease, can they be relied on in practice? A recent exhaustive meta-analysis published by Glasgow et al.[12] attempted to determine the reliability of the aforementioned factors in predicting nodal disease. This study included data from 76 articles but mixed both colon and rectal cancers. However, they did perform a subset analysis for rectal cancer. In looking at 12 different pathologic features in rectal tumors, the strongest predictors of nodal involvement were tumor budding [OR = 5.8 (4.8–7.1)] and poor differentiation at the invasive front [OR = 6.1 (3.9–9.5)]. Interestingly, T stage (T1 vs. T2) was not the strongest predictor, with an odds ratio of 2.6 (2.33–2.9). Overall differentiation, lymphatic invasion, and vascular invasion also showed statistically significant odds ratios [2.68 (2.5–2.87), 3.63 (2.66–4.95), and 2.63 (1.76–3.91), respectively]. Their conclusion based on the review of all existing literature was that the poor predictive value of many of the most commonly reported histopathologic characteristics of rectal tumors are “no better than a coin flip at