



Lymph Node Metastasis, Radical Surgery, and Prognosis in Well-Differentiated Neuroendocrine Tumors of the Rectum

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The optimal management of localized and well-differentiated neuroendocrine tumors (NETs) of rectal origin is uncertain and complicated. At this time, treatment decisions are driven largely by expert consensus opinion. In the National Comprehensive Cancer Network (NCCN) guidelines, there are several indications to manage rectal NETs with only endoscopic resection, including (1) small (< 1 cm) incidental tumors completely resected with negative margins, (2) small (< 1 cm) incidental tumors completely resected with indeterminate margins that are low grade and with no residual disease on subsequent follow-up endoscopy at 6–12 months, and (3) other rectal NETs with no invasion into the muscularis propria (T1) or tumors that are ≤ 2 cm with no lymph node (LN) metastasis in clinical assessment.¹ Radical surgery [either low anterior resection (LAR) or abdominoperineal resection (APR)] is the standard approach for any rectal NET with muscularis propria invasion (T2–T4) that is (1) > 2 cm in size or (2) node positive.¹ Importantly, at this time, there is no imaging standard for clinical LN assessment, with options including both abdominal/pelvic multiphasic computed tomography (CT) and abdominal/pelvic magnetic resonance imaging (MRI); the decision to pursue nuclear imaging [i.e., Gallium-68 DOTATATE positron emission tomography (PET)/CT or PET/MRI to identify the somatostatin receptor] for LN assessment is at the discretion of the treatment team.¹ Of note, while the NCCN guidelines do not specifically mention the presence of lymphovascular invasion (LVI) as a risk factor for lymph node metastases in

rectal NETs, in clinical practice, the presence of LVI is also considered in decision making for surgery.

While the presence of clinical node-positive disease impacts our decision making with regards to radical surgery for rectal NETs, prior efforts have not consistently (1) identified and validated risk factors for LN metastasis and (2) demonstrated the impact of LN metastasis and/or resection on prognosis.

In the paper, “Risk factors for lymph node metastasis of rectal neuroendocrine tumor and its prognostic impact: a single-center retrospective analysis of 195 cases with radical resection,” Hiyoshi et al. present the results from a large retrospective analysis of rectal NETs with radical resection in an effort to improve knowledge of these two topics.² The authors evaluate many high-risk features of rectal NETs, and through their work, validate three factors—venous invasion, a clinical node-positive status, and the presence of multiple primary rectal NETs—as independent predictors of LN metastasis. In survival analysis, Hiyoshi et al. investigated the prognostic impact of LN metastasis, and found that the presence of LN metastasis was significantly associated with poorer prognosis (specifically, shorter disease-free and disease-specific survival).

There are important takeaways from this work. As all patients underwent radical surgery, the findings from this study add to our growing understanding of LN metastasis in rectal NET. Hiyoshi et al.’s findings are consistent with prior investigation, demonstrating an increase in LN metastasis rate as tumor size increases.³ However, a particularly interesting finding comes from Hiyoshi et al.’s evaluation of LN metastasis in < 1 cm size tumors, where they observed a LN metastasis rate of 22% in tumors < 0.5 cm in size and 32% in tumors 0.5–1 cm in size; importantly, as this study included those rectal NETs that were recommended for radical surgery, these small rectal NETs also harbored other risk factors for LN metastasis, and thus, as acknowledged by the authors, the rate of LN metastasis is likely overestimated

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in this cohort of rectal NETs < 1 cm in size. At this time, for small < 1 cm rectal NETs, the presence of additional risk factors is not widely considered for treatment decision making; given the association of LN metastasis with poorer prognosis, and the presence of LN metastasis in these small rectal NETs with additional risk factors, further investigation is warranted in this rectal NET subset to advise of the best treatment approach, perhaps specifically in those rectal NETs with venous invasion or LVI, which has been demonstrated in this study and others, to have an impact on LN metastasis.^{4,5}

While not emphasized in the paper by Hiyoshi et al., perhaps one of the most valuable findings from this work is the benefit of radiologic assessment with MRI versus CT in clarifying rectal NET clinical node status. In this surgical series, in the 195 patients that underwent radical surgery, 70 (36%) underwent preoperative CT and 125 (64%) underwent CT/MRI; the sensitivity for LN diagnosis was 17% in the CT group, and improved to 42% in the CT/MRI group. Taken together, the results suggest a potential benefit of MRI over CT alone to evaluate rectal NET clinical node status. In future work, this observation should be further investigated.

While Hiyoshi et al. demonstrate the worse prognosis of rectal NETs that involve the LNs, a therapeutic advantage for LAR/APR radical surgery in these patients remains unknown. In their conclusions, Hiyoshi et al. propose a randomized controlled trial to investigate long-term outcomes after local resection with follow-up alone without additional treatment versus radical surgery with accompanying LN dissection in patients with rectal NETs with risk factors for LN metastasis. While this type of prospective trial would certainly add to our body of knowledge, we must also consider the proposed study with the understanding that in 2023, there is no available postoperative/adjuvant therapy to offer our patients with node-positive rectal NETs. Additionally, at this time there are no planned studies of adjuvant therapy for this disease.

In other diseases, such as melanoma with known sentinel node metastases, completion lymph node dissection, when compared with observation, did not increase disease-specific survival, and was associated with more morbidity.^{6–8} Similarly, in breast cancer involving the sentinel nodes, the use of sentinel lymph node dissection, in comparison to axillary lymph node dissection, was not associated with worse survival.^{9,10} Importantly, in these other cancers, unlike rectal NET, let alone any NET, there are postoperative therapies to offer for the eradication of micro-metastatic disease, with proven associated survival benefits after use of those treatments. Thus, in those diseases, the sampling of the nodes is important for therapeutic consideration. While the study proposed by Hiyoshi et al. is interesting and perhaps could answer the question of whether there is a therapeutic

advantage to radical surgery, I question the feasibility and utility, particularly in the absence of active adjuvant therapy for rectal NETs and the associated morbidity for our patients.

DISCLOSURES The author declares no conflict of interest.

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