Editorial

The quandary of N0 disease after neoadjuvant therapy for rectal cancer

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Improved outcomes after curative resection for rectal cancer have been driven in part by total mesorectal excision (TME) and the introduction of neoadjuvant chemoradiation. An equally important consideration in optimizing prognosis is accurate pathological staging, which is highly dependent on accurate assessment of lymph node status after TME. The use of neoadjuvant treatment impacts lymph node harvests and affects pathologic staging.

Based on the anatomy of tumor cell spread along lymphatic pathways, Halsted was the first to suggest that en-bloc excision would provide the best chance of local and distant cancer control (1). This provides the basis of TME technique, as sharp dissection along the mesorectal fascia yields the entire mesorectum, which is the lymph node-bearing mesentery of the rectum. Secondarily, it removes any small regional metastases. Removing lymph nodes with the surgical specimen removes cancer cells, but more importantly provides information about staging, prognosis, and guides treatment decisions. For example, the United States Surveillance, Epidemiology and End Results (SEER) cancer registry database shows that for each T stage, 5-year overall and disease-free survival decreases with increasing LN involvement. The presence of lymph node metastases determines the patients most likely to benefit from adjuvant therapy (2).

The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUAC) recommends removing at least 12 lymph nodes to properly assess the adequacy of surgical resection and provide adequate information for staging. Having a minimal lymph node cut off value is problematic as the number of lymph nodes is highly individual, varying with age, location, and tumor characteristics such as growth factors and microsatellite instability. Even with standardized surgical technique and pathologic evaluation (including the use of fat clearing to optimize lymph node harvest), the total number of lymph nodes harvested after neoadjuvant chemoradiation is highly variable and frequently less than 12, and with the possibility of fewer positive lymph nodes, downstaging can occur (3,4). To address this issue, we previously proposed calculating lymph node ratios as a method that incorporates the negative impact on survival of finding as few as one positive lymph node and the uncertainty regarding the optimal number of total lymph nodes to harvest (5). This lymph node ratio is valuable as an independent prognostic factor for overall survival, not only in rectal cancer, but also in gastric, breast, bladder, pancreatic cancer, and colon cancer (6).

Interestingly, increasing the number of lymph nodes retrieved is associated with increased survival among patients with colorectal cancer (7,8). The article by Denham and colleagues in the current issue of the *Journal of Gastrointestinal Oncology* provides a wide-ranging review of multiple studies and biologic principles to determine the underlying basis of this observation. Given the lack of consensus in the literature, the authors conclude that the explanation for the association of increased survival with increased lymph node retrieval is multifactorial and lies in tumor-host biology (9).

Clinically, deciding how many lymph nodes to retrieve is less relevant, as a surgeon performing a "cancer operation" should, by virtue of optimal surgical technique, maximize the mesenteric lymph nodes harvested. The implication of a positive lymph node is clear. However, what information can we derive from a surgical specimen that does not yield any positive nodes, especially after neoadjuvant chemoradiation? Lack of positive lymph nodes can be the result of inadequate surgical technique, inadequate pathological examination, or more encouragingly, reflect a robust tumor response to treatment. The implication for patients who undergo neoadjuvant therapy with complete TME and have pathologically negative lymph nodes is still unclear, as some

studies suggest that the reduced total lymph node yield has no prognostic impact on overall survival (10) while other studies show that increasing the number of negative lymph nodes examined is correlated with decreased recurrence and increased cancer-specific survival (11).

The authors offer an algorithm that demonstrates the negative predictive value of lymph nodes based upon the number of lymph nodes sampled. Sampling 12-15 lymph nodes produces a negative predictive value of 78-83%. In combination with lymph node ratios, the ability to predict confidence in a lymph node sample may be valuable for accurate staging. At this point, further consensus is needed to make treatment decisions based on current staging ability. Further studies are needed to determine whether patients who undergo complete TME and have adequate negative lymph node harvest can forego post-operative chemotherapy. Surgeons can do their part to provide a more complete oncologic picture by using techniques that optimize lymph node harvests.

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