

## Lymph Node Yield and Oncologic Outcome after Colorectal Cancer Resection

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When performing mesorectal and mesocolic excision for rectal and colon cancer, it is crucial to encompass the draining nodal basins for staging and, possibly, therapeutic purposes. During the past 15 years, colorectal cancer investigators have demonstrated a relationship between the number of lymph nodes examined in the surgical specimen and oncologic outcome. However, the nature of this relationship has not been clearly elucidated. Early explanations for this finding were based on the concept of understaging.<sup>1</sup> The hypothesis was that with fewer nodes examined, the pathologist was less likely to identify metastatic nodes and the patient would be given an inappropriate diagnosis of stage I or II rather than stage III cancer. However, the linear relationship between the total number of lymph nodes in the specimen and the number of metastatic lymph nodes argues against understaging as the primary explanation.<sup>1–3</sup> If understaging was the cause of this phenomenon, the number of positive nodes would plateau at a certain number of total lymph nodes examined. Yet, multiple investigators have been unable to demonstrate that there is a number above which examination of additional lymph nodes does not identify more metastatic nodes.

Many authors have hypothesized that maximal surgical clearance of metastatic lymph nodes offers therapeutic effect. Although this may be intuitive, mesenteric lymph node recurrence is a very uncommon phenomenon, and this hypothesis remains unsupported. Kanemitsu et al. have attempted to use their results to support the practice of central vascular pedicle ligation. However, they state that it is standard practice in Japan to resect apical nodes if the stage is T2 or higher; in this study there is no control group without proximal ligation. As a result, such an assumption

cannot be supported by these data nor is there conclusive evidence elsewhere in the existing colorectal cancer literature that proximal pedicle ligation improves oncologic outcome or is necessary for adequate lymph node yields. In a study, conducted by this author, of a consecutive series of surgical specimens at a single center, apical vessel ligation was not universally performed; yet 96 % of the specimens were found to contain more than 12 lymph nodes.<sup>4</sup> Meticulous surgical technique and careful pathologic examination is paramount to achieve high lymph node yields. Many protocols have been advocated to maximize nodal yield, including the use of *in vivo* or *ex vivo* dye injection, fat clearance, and multiple rounds of gross examination.<sup>4–6</sup> However, one cannot categorically state that specific surgical or pathologic methods are necessary to achieve such yields in all cases, because this has not been adequately studied in a prospective, controlled fashion.

Kanemitsu et al. have elegantly demonstrated that, in a broad population of stage II colorectal cancer patients, the threshold of 12 lymph nodes examined is associated with superior predictive capacity for prognosis in individual patients. Moreover, they acknowledge that this association is not straightforward. However, their discussion focuses on improved staging and clearing of micrometastatic disease, neither of which has been proven causal despite almost two decades of investigation. Biologic explanations need to be examined further. Age, tumor size, depth of penetration, location, use of radiation, and gene mutations have been associated with lymph node yield.<sup>4,7–9</sup> These findings suggest a host–tumor interaction that may result in stimulation of the immune system and, as a consequence, larger and thus easier to identify mesenteric lymph nodes. It does not stretch the imagination to consider that such an interaction would have implications for tumor recurrence. Our understanding of the biology of lymph node hypertrophy or proliferation in the presence of a colorectal

adenocarcinoma remains limited. Investigation of this response to tumors may reveal important aspects of the body's barriers to metastatic progression.

The threshold of 12 lymph nodes may have prognostic implications; however, rather than implicating the surgeon's or pathologist's efforts to find lymph nodes as inadequate, the underlying mechanism may relate more to an individual cancer patient's inability to mount an effective immune response to his or her tumor, or other biologic explanations. The relationship between lymph node yield and prognosis is far more complicated than we currently understand. This is highlighted by a paradoxical finding in one study in which a higher number of lymph nodes examined was associated with worse survival in a subpopulation of patients with high lymph node ratio (number of positive lymph nodes/total number of nodes).<sup>10</sup> Given the need for medical oncologists to stratify stage II colon cancer patients as high risk and low risk when considering use of adjuvant therapy, low lymph node yield remains clinically relevant. Further support for selecting a threshold is that population studies have revealed that many hospitals are reporting low median lymph node yields.<sup>7, 11</sup> Having such a threshold allows for a quality benchmark for institutions. Consequently, it is reasonable for surgeons and pathologists to strive to remove and identify more than 12 lymph nodes whenever possible, while accepting that in a small number of colon cancer patients and a large number of rectal cancer patients treated with neoadjuvant therapy there will be fewer than 12 lymph nodes in the surgical specimen. Until we better understand this finding, we should consider low lymph node yields in individual colon cancer patients as a marker and not a cause of higher risk of recurrence.

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