

Separating Surgical Quality From Causality—Gaining Perspective in the Debate on Lymph Node Count and Extent of Lymphadenectomy

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For several cancers, the number of lymph nodes removed and the extent of lymphadenectomy are associated with survival.^{1–3} Although largely based on observational studies, this association has permeated surgical thinking, and considerable debate regarding the importance of lymph node count and extent of lymphadenectomy has emerged in many surgical circles. For bladder cancer, in which a growing number of studies have outlined the association between increasing lymph node count and survival,^{4,5} the debate has gained traction more recently. During the development of this discourse, however, several of the central components of the debate have become entangled. Consequently, distinctions between association, causation, and quality have been blurred.

In this issue of *Cancer*, Wright and colleagues set out to further inform the debate in a detailed and thorough observational study.⁶ Using data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, the authors examine the association between extent of lymphadenectomy, as measured by lymph node count, and survival in the setting of lymph node-positive bladder cancer. They report an independent, inverse correlation between the number of lymph nodes removed and the risk of death for each category of lymph node count analyzed. In cases characterized by relatively low lymph node counts (1–5 lymph nodes), for example, median survival was 13 months, and increased proportionately with each incremental increase in lymph node count, reaching 23 months in cases where ≥ 10 lymph nodes were removed during cystectomy. Lymph node density, a derivative measure of disease burden (the number of positive lymph nodes divided by the total number of lymph nodes) also correlated significantly with survival. After adjusting for measurable patient-level factors, patients who had ≥ 10 lymph nodes removed during cystectomy were nearly half as likely to die compared with patients who had 5 lymph nodes removed at the time of surgery (hazard ratio, 0.52; 95% confidence interval, 0.43–0.64). On the basis of these results, the authors conclude that lymph node count is independently asso-

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ciated with survival in the setting of lymph node metastases and suggest that their results support the role of extended lymphadenectomy in the surgical management of invasive bladder cancer.

Although Wright et al. correctly acknowledge several potential study limitations, the extent of methodological and data-related shortcomings severely undercut the principal inference that more extensive lymphadenectomy mediates survival after cystectomy. Consequently, the findings of their observational study, like those from other observational studies concerning this issue in other cancer settings, are inherently flawed and should not be interpreted without carefully drawing a line between association and causation. Several issues warrant consideration here. Perhaps most apparent, the authors' use of total lymph node count as a proxy measure for extent of lymphadenectomy is problematic. Although the 2 are correlated, the strength of the correlation is not known and may be marginal secondary to variation within and between surgeries, surgeons, pathologists, and institutions. The distinction is important. Although expanding anatomic boundaries undoubtedly increases lymph node retrieval, other factors, such as biologic differences between individuals, thoroughness of the dissection, and pathologic processing, may be more important, even in settings of limited or standard lymphadenectomy. Consequently, it is unclear whether the authors are able to estimate the extent of lymph node dissection.

Perhaps more important, the absence of relevant clinical information is problematic. Although SEER provides detailed information regarding cancer characteristics, the lack of noncancer-related medical information precludes any adjustment for case mix. As a result, Wright et al. are unable to reliably establish that patients managed according to various degrees of lymph node removal are similar or dissimilar in terms of health status, concomitant medical conditions, and burden of illness. Without question, such factors impact intraoperative decision making and probably are related to both the extent of surgical dissection and survival. Accordingly, the extent of lymphadenectomy may be impacted significantly by a patient's physiologic health and level of infirmity, resulting in differential probabilities of extended lymphadenectomy according to unmeasured patient-level factors. The resulting confounding by indication is crippling, because the attribution of the observed difference in survival cannot be assigned to the number of lymph nodes removed with any certainty. It is just as likely, if not more so, that the observed differences result from crucial, unmeasured factors that discriminate between patients who are

more likely to undergo a thorough lymph node dissection and those who are not.

Additional limitations are threatening. In particular, antecedent and subsequent perioperative processes of care cannot be accounted for in this analysis. Most notably, information regarding the use of chemotherapy was not available to the authors, raising additional concerns related to the possible impact of neoadjuvant and adjuvant therapy on survival time and the potential for differential use of chemotherapy according to health status. Confounding by indication is not uncommon in observational studies that compare different treatments and patient groups, even in circumstances in which more detailed information is available for risk adjustment.⁷⁻⁹ Beyond the problematic issue of residual confounding in such cases, limiting the threat of unbalanced group comparison is fundamental when contrasting treatment outcomes.¹⁰ In the study by Wright et al., unfortunately, even basic adjustment was not possible.

Are lymph node counts associated with survival? Yes, but causality is less clear and has not been established reliably. Some clinicians have gravitated toward a potential therapeutic effect resulting from the surgical clearance of micrometastases. Equally, if not more plausible explanations, including more accurate staging, guidance of downstream adjuvant therapies, and differential selection based on health status, have been relatively discounted. In gastric cancer, in which the association has been examined in several large-scale, randomized surgical trials, extending lymph node dissections does not extend survival.¹¹⁻¹³ Furthermore, other data exploring similar correlations for bladder¹⁴ and colon¹⁵ cancer demonstrate a much more limited impact after accounting for patient and hospital differences.

Still, the number of lymph nodes removed during cancer surgery may be related to surgical quality at some level. Certainly, few surgeons would argue that the variation in lymph node counts is not influenced partially by surgical quality or that the attendant accuracy in cancer staging is unimportant. The debate has now evolved toward benchmarks. Currently, the National Quality Forum, in collaboration with the American College of Surgeons, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network, has moved toward minimum lymph node count thresholds as measures of quality for several cancers. Unfortunately, focusing on an absolute count may undermine the principal objective and marginalize the overall impact of the quality effort.¹⁵ Even at recognized centers of excellence, lymph node counts vary substantially, and

proposed thresholds may not always be achieved,⁵ raising additional questions regarding the utility of minimum counts. Arguably, decreasing the number of under-staged cancer cases secondary to inadequate or absent lymphadenectomy¹⁶ is a more important quality objective. Although the vehicle for improvement remains unclear and the debate regarding quality and lymph node count will continue, surgeons should not confuse the association between lymph node count and survival with a cause-and-effect relation. That piece of the debate should turn to gathering more reliable, less confounded information.

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