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. 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, 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. 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-
ociated with survival in the setting of lymph node me-
tastases 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 sev-
eral potential study limitations, the extent of metho-
dological and data-related shortcomings severely
undercut the principal inference that more extensive
lymphadenectomy mediates survival after cystec-
tomy. Consequently, the findings of their observa-
tional study, like those from other observational
studies concerning this issue in other cancer set-
tings, are inherently flawed and should not be inter-
preted 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 problem-
atic. Although the 2 are correlated, the strength of the
correlation is not known and may be marginal sec-
tary to variation within and between surgeries, sur-
geons, pathologists, and institutions. The distinction
is important. Although expanding anatomic bound-
aries undoubtedly increases lymph node retrieval,
other factors, such as biologic differences between
individuals, thoroughness of the dissection, and path-
ologic 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 char-
acteristics, the lack of noncancer-related medical
information precludes any adjustment for case mix.
As a result, Wright et al. are unable to reliably estab-
lish 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 signifi-
cantly by a patient’s physiologic health and level of in-
firmity, 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 cer-
tainty. 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 dis-
section and those who are not.

Additional limitations are threatening. In parti-
cular, 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. Confound-
ing by indication is not uncommon in observational
studies that compare different treatments and pa-
tient groups, even in circumstances in which more
detailed information is available for risk adjust-
ment.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 simi-
lar correlations for bladder14 and colon15 cancer
demonstrate a much more limited impact after account-
ning for patient and hospital differences.

Still, the number of lymph nodes removed dur-
ding 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 influ-
enced partially by surgical quality or that the attend-
ant accuracy in cancer staging is unimportant. The
debate has now evolved toward benchmarks. Cur-
rently, the National Quality Forum, in collaboration
with the American College of Surgeons, the American
Society of Clinical Oncology, and the National Com-
prehensive Cancer Network, has moved toward mini-
imum 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 excel-
ence, lymph node counts vary substantially, and
proposed thresholds may not always be achieved, raising additional questions regarding the utility of minimum counts. Arguably, decreasing the number of under-staged cancer cases secondary to inadequate or absent lymphadenectomy 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.

REFERENCES