Number of Lymph Nodes Removed and Survival after Gastric Cancer Resection: An Analysis from the US Gastric Cancer Collaborative

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BACKGROUND: Examination of at least 16 lymph nodes (LNs) has been traditionally recommended during gastric adenocarcinoma resection to optimize staging, but the impact of this strategy on survival is uncertain. Because recent randomized trials have demonstrated a therapeutic benefit from extended lymphadenectomy, we sought to investigate the impact of the number of LNs removed on prognosis after gastric adenocarcinoma resection.

STUDY DESIGN: We analyzed patients who underwent gastrectomy for gastric adenocarcinoma from 2000 to 2012, at 7 US academic institutions. Patients with M1 disease or R2 resections were excluded. Disease-specific survival (DSS) was calculated using the Kaplan-Meier method and compared using log-rank and Cox regression analyses.

RESULTS: Of 742 patients, 257 (35%) had 7 to 15 LNs removed and 485 (65%) had $\geq$16 LNs removed. Disease-specific survival was not significantly longer after removal of $\geq$16 vs 7 to 15 LNs (10-year survival, 55% vs 47%, respectively; $p = 0.53$) for the entire cohort, but was significantly improved in the subset of patients with stage IA to IIIA (10-year survival, 74% vs 57%, respectively; $p = 0.018$) or N0-2 disease (72% vs 55%, respectively; $p = 0.023$). Similarly, for patients who were classified to more likely be "true N0-2," based on frequentist analysis incorporating both the number of positive and of total LNs removed, the hazard ratio for disease-related death (adjusted for T stage, R status, grade, receipt of neoadjuvant and adjuvant therapy, and institution) significantly decreased as the number of LNs removed increased.

CONCLUSIONS: The number of LNs removed during gastrectomy for adenocarcinoma appears itself to have prognostic implications for long-term survival. (J Am Coll Surg 2015;221:291–299. © 2015 by the American College of Surgeons)

Gastric adenocarcinoma is the second leading cause of cancer-related death worldwide.[1] Resection of the primary tumor with appropriate dissection of surrounding lymph nodes (LNs) is the foundation of curative-intent therapy. The optimal extent of lymphadenectomy has been the subject of a longstanding and contentious debate. In general, D1 node dissection includes perigastric LNs within 3 cm from the primary tumor, D2 extends the dissection

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Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
DSS = disease-specific survival
HR = hazard ratio
LN = lymph nodes
(r) = ratio of positive to removed lymph nodes

beyond D1 to include LNs around the hepatic and splenic arteries (with distal pancreatectomy and splenectomy advocated for proximal gastric tumors), and D3 dissection further includes LNs in the root of the mesocolon, retropancreatic, and para-aortic areas. In Asia, D2 lymphadenectomy has been traditionally regarded as the gold standard yielding remarkable long-term survival rates in single-arm studies.[2] However, 2 prospective randomized trials carried out in the United Kingdom[3,4] and the Netherlands[5,6] in the early 1990s failed to identify a survival advantage of D2 over D1 lymphadenectomy. The sizeable perioperative mortality in the D2 arm of these trials (13% and 10%, as opposed to 6.5% and 4%, respectively, for the D1 arm), largely attributed to the routine performance of distal pancreatectomy and splenectomy, was thought to perhaps offset any potential survival benefit provided by the more radical surgery. However, more recently, the Italian Gastric Cancer Study Group demonstrated that Western surgeons can perform D2 dissections with very low mortality (2.2%),[7] and Japanese surgeons have embraced pancreas-preserving D2 dissections as equally effective as pancreas-sacrificing ones.[8] Furthermore (although there is no proven superiority of D3 over D2 dissection),[9] a recent randomized trial from Taiwan demonstrated a statistically significant survival advantage associated with D3 vs D1 dissection,[10] and the most recent update of the Dutch trial showed D2 dissections to be associated with a lower disease-related death rate (37% vs 48%) after a median follow-up of 15 years.[11]

It is intuitive that a more extensive node dissection will harvest more LNs to be examined pathologically, further improving stage assignment. However, the contribution of a higher LN count to improved locoregional disease control and possibly, survival after gastric cancer resection, has not been consistently demonstrated. In addition, the optimal number of LNs to be examined in order to ensure staging accuracy, and perhaps offer a hypothetical therapeutic benefit, is not well established. This number has been suggested to be 10,[12,13] 15,[14,15] or even 25.[16] In 1997, the American Joint Committee on Cancer (AJCC) redefined N stage in gastric cancer as N1, 1 to 6 positive LNs; N2, 5 to 7 positive LNs; and N3, ≥16 positive LNs.[17] Therefore, it was recommended that a minimum number of 16 LNs should be evaluated to ensure accurate staging, simply as the lowest denominator necessary to stage a patient as N3. Of note, the most recent 2009 revision of the AJCC staging system has reclassified the N categories as N1, 1 to 2 positive LNs; N2, 3 to 6 positive LNs; and N3, ≥7 positive LNs.[18]

Given recent evidence from randomized trials suggesting a long-term, disease-specific survival benefit from extended node dissection during resection of gastric adenocarcinoma,[10,11] the goal of this analysis was to use a modern, multi-institutional database of US patients and examine whether the total LN count correlates with survival after gastric cancer resection, whether 16 LNs remains the optimal threshold, and whether a specific subset of gastric cancer patients are more likely to benefit from a higher number of LNs removed.

METHODS

The study cohort included consecutive patients who underwent surgical resection for gastric adenocarcinoma between 2000 and 2012 at 7 academic medical centers participating in the US Gastric Cancer Collaborative: Emory University, Johns Hopkins University, Stanford University, The Ohio State University, University of Wisconsin, Wake Forest University, and Washington University in St Louis. Patients who underwent R2 resection or had M1 disease at operation were excluded from this analysis. Data on patient demographics, clinicopathologic and intraoperative variables, perioperative outcomes, and disease-specific survival (DSS) were retrospectively collected after Institutional Review Board approval at each participating site. Surgical complications were graded using the modified Clavien-Dindo classification.[19]

Categorical variables were presented as absolute counts (percentages) and compared using the Fisher exact test or chi-square tests. Continuous variables were presented as means (standard deviation, SD) and compared using the *t*-test. Disease-specific survival was measured from the time of resection to death from gastric cancer or last follow-up. Survival probabilities were calculated using the Kaplan-Meier method and compared using the log-rank test. A 2-sided p value < 0.05 was considered statistically significant.

We anticipated that a major source of bias in our analysis would be related to the effect of stage migration, as a mechanism leading to seemingly superior survival after removal of more LNs. In other words, patients with fewer LNs removed could be inappropriately "understaged" and imprecisely compared with patients belonging in more favorable groups. We used 2 specific strategies to account for this potential bias. First, we excluded patients who had