HHS Public Access
Author manuscript
J Am Coll Surg. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:
J Am Coll Surg. 2015 August ; 221(2): 291–299. doi:10.1016/j.jamcollsurg.2015.04.024.

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

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Abstract

Background—Examination of at least 16 lymph nodes (LNs) has been traditionally recommended during gastric adenocarcinoma (GAC) resection to optimize staging, but the impact of this strategy on survival is uncertain. As 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 GAC resection.

Study Design—Patients who underwent gastrectomy for GAC from 2000 to 2012 at seven US academic institutions were analyzed. 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 7–15 LNs removed and 485 (65%) had ≥16 LNs removed. DSS was not significantly longer after removal of ≥16 versus 7–15 LNs (10-year, 55% versus 47%; P = 0.53) for the entire cohort, but was significantly improved in the subset of patients with stage IA-IIIA (10-year, 74% versus 57%; P = 0.018) or $N_{0\text{-}2}$ disease (72% versus 55%, P = 0.023). Similarly, for patients who were classified to more likely be "true $N_{0\text{-}2}$", 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, as well as institution) significantly decreased as the number of LNs removed increased.

Conclusions—The number of lymph nodes removed during gastrectomy for adenocarcinoma appears itself to have prognostic implications on long-term survival.

INTRODUCTION

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 beyond D1 to include LNs around the hepatic and splenic artery (with distal pancreatectomy and splenectomy advocated for proximal gastric tumors), and D3 dissection further includes LNs in the root of 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, two 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 felt 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 with 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 assure 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 N_1: 1–6 positive LNs, N_2: 7–5 positive LNs, and N_3: ≥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 N_3. Of note, the most recent 2009 revision of the AJCC staging system has reclassified the N categories as N1: 1–2 positive LNs, N_2: 3–6 positive LNs, and N_3: ≥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 the present analysis was to utilize 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 includes consecutive patients who underwent surgical resection for gastric adenocarcinoma between 2000–2012 at seven academic medical centers participating in the U.S. 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 the present analysis. Data on patient demographics, clinicopathologic and intraoperative variables, as well as perioperative outcomes and disease specific survival (DSS) were retrospectively collected following Institutional Review Board approval the 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. DSS 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 two-sided P value of < 1.5 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 to patients belonging in more favorable groups. We utilized two specific strategies to account for this potential bias. First, we excluded patients who had 0 to 6 LNs examined from our univariate analysis, as having ≥ 7 positive LNs defines N_3 disease in the latest 7th edition of the AJCC staging system. This way we assured that every patient in the study could at least in theory have the potential for accurate staging. Second, when fitting a Cox proportional hazards model examining the adjusted hazard ratio (HR) of disease-related death as a function of the number of LNs removed, we created two broad stage categories [S_0 (less advanced) stage and S_1 (more advanced) stage]. These two stage categories reflect whether a patient is truly $N_{0\text{-}2}$ versus N_3, based on the true (but not necessarily the observed) ratio of positive to removed LNs, r (S_0 when $r < 7/16$, S_1 when $r \geq 7/16$). The assignment to the S_0 or S_1 group does not depend on how many LNs were actually removed during surgery. These two groups are virtually unobservable, given the fact that the number of LNs removed per patient is variable and, by definition, never sufficient to compute r exactly. We therefore created two observable groups [$\hat{S}_0$ (more likely true $N_{0\text{-}2}$) and $\hat{S}_1$ (more likely true N_3)], based on the probability of a patient being S_0 or S_1, conditional on both the number of positive LNs and the total number of LNs removed in each case. The probability of being a true S_1 ($r \geq 7/16$), p was computed using the Bayes’ rule, the prior distribution for r, and the binomial likelihood. The prior distribution for r was estimated from the data using deconvolution on the binomial distribution.[20] Note that this analysis is not Bayesian, but in fact fundamentally frequentist, as the prior distribution and the rest of the analysis is entirely determined objectively and empirically from the observed frequencies. $\hat{S}_0$ represents patients with $p < 0.5$ (more likely true $N_{0\text{-}2}$), while S_1 represents patients with $p \geq 0.5$ (more likely true N_3). Our $\hat{S}$ classification attempts to counteract the stage migration problem by explicitly incorporating information about both number of positive LNs and total number of LNs removed. Thus, removing more LNs from a given patient could result in a higher or lower $\hat{S}$ stage allocation, depending on the number of new positive LNs (unlike with traditional N-staging, in which removing more nodes can only raise a patient's stage). We emphasize that we are not just using the observed LN ratio (positive/total), but the probability of the true ratio being above some threshold, which incorporates information about the confidence in the ratio (e.g. an observed ratio of 75% is treated differently if it is 3/4 than if it is 30/40).

RESULTS

From 2000 to 2012, 965 patients with gastric adenocarcinoma underwent surgical resection at one of seven academic institutions participating in the U.S. Gastric Cancer Collaborative. After excluding 101 patients with M1 disease at surgery and 5 patients who underwent R2 resections, the remaining 859 patients had a mean of 19 LNs removed (SD 11, median 17, IQR 11–25). Of those, 117 patients had 0 to 6 LNs examined and were excluded from initial (univariate) analysis. Of the remaining 742 patients, 257 (35%) had 7–15 lymph nodes removed and 485 (65%) had ≥ 16 lymph nodes removed. A comparison of clinical, intraoperative, pathologic, and postoperative variables between the 2 groups appears in Table 1. Older patients tended to have fewer LNs removed, but otherwise there were no differences in demographics, comorbidities, or frequency of neoadjuvant chemotherapy. Patients who had ≥ 16 LNs removed were more frequently described to have a D2 versus D1 lymphadenectomy, however this did not translate into higher rates of pancreatectomy or splenectomy (likely due to popularity of a "modified", spleen and distal pancreas-preserving D2 dissection in the US), longer operative time, higher blood loss or more frequent blood transfusion. Similarly, the two groups had a similar incidence and severity of postoperative complications, length of hospitalization, readmission and in-hospital mortality rates. There were no differences in resection margin status and grade between the two groups, however patients with ≥16 LNs removed had tumors of more advanced T and N stage.

When the entire cohort of 742 patients was examined, patients with ≥ 16 LNs removed did not have a significantly improved DSS after resection (10-year 55% vs. 47%, P = 0.53, Figure 1). On further subset analysis stratified by AJCC stage (Figure 2), again no specific group had a statistically significant improvement is DSS after removal of ≥ 16 LNs. However, there appeared to be a trend towards improved survival after removal of ≥ 16 LNs in earlier stages (I-A through III-A). In fact, when patients of stages I-A through III-A were combined, removal of 16 or more LNs was associated with improved DSS (10-year 74% vs. 57%, P = 0.018). This survival difference was not observed in stages III-B and III-C (P = 0.55, Figure 3). Similarly, in a subset analysis based on N stage, patients with $N_{0\text{-}2}$ disease appeared to have improved DSS after removal of at least 16 LNs (10-year 72% vs. 55%, P = 0.023), whereas patients with N_3 disease did equally poorly, irrespective of the number of LNs removed (P = 0.882, Figure4).

Last, a Cox proportional hazards model was fitted to calculate the HR for disease-specific death as a function of the total number of LNs removed, with the latter now being analyzed as a continuous variable. The rationale behind this analysis was two-fold: first, to control for additional factors in a multivariate fashion, and second to assess the optimal LN count threshold that is potentially associated with the highest survival benefit. The HR was adjusted for T stage, margin status, and grade (as established pathologic predictors of survival after resection of gastric cancer) as well as administration of neoadjuvant therapy, receipt of any adjuvant therapy, and institution (to account for potentially different institutional practices). This second phase of our analysis included patients who had 1 or more LNs removed and used 0 LNs as the reference point. The HR was not adjusted for N stage, as two relevant stage groupings ($\hat{S}_0$ and $\hat{S}_1$) were created as described in the Methods section. As shown in Figure 5, a significant improvement in the HR was noted as more LNs were removed in less advanced stage patients ($\hat{S}_{0,}$ more likely to be true $N_{0\text{-}2}$, n = 676). In this group, the HR kept improving as the number of LNs removed increased up to 16, but there did not appear to be an incremental improvement in the HR beyond this threshold. In contrast, in more advanced patients ($\hat{S}_{1,}$ more likely to be true N_3, n = 163), the number of LNs removed had no influence on the HR.

DISCUSSION

Based on this large, modern cohort of gastric cancer patients from seven U.S. academic institutions, we observed that survival after gastrectomy was improved when 16 or more LNs were removed in all, except advanced stage, patients. In advanced stage patients (III-B and III-C or N_3), tumor stage adversely dominated outcome irrespective of the number of LNs removed. When the entire cohort of patients was examined, we found an 8% improvement in DSS probability at 10 years (Figure 1), which was not statistically significant, but still very reminiscent of the 11% (and statistically significant) DSS improvement noted in the recently reported 15-year follow-up of the Dutch D1 versus D2 randomized trial.[11] We found no incremental improvement in the adjusted HR for DSS beyond removing 16 LNs (in patients with less advanced tumors), although due to the relatively wide confidence intervals in Figure 5, this finding should be interpreted with caution.

The notion that the number of LNs removed during gastric cancer resection might have prognostic significance is not novel and has been previously suggested. A SEER analysis of 3,814 patients showed overall survival following gastric cancer resection to be highly dependent on the number of LNs examined.[13] For every 10 additional LNs dissected beyond the first one, 5-year survival improved by 7.6% in $T_{1/2}N_0$ patients, 5.7% in $T_{1/2}N_1$, 11% in T_3N_0, and 7% in T_3N_1. In keeping with our findings, this study did not analyze patients with stages more advanced than T_3N_1, beyond which one would expect the advanced stage of the tumor to determine outcome, irrespective of the number of LNs removed. Similarly, the prospective multicenter German Gastric Cancer Study of 1,654 patients showed that dissection of > 25 LNs had a significant and independent effect on survival in patients with stage II tumors.[16] Last, in the Memorial-Sloan Kettering nomogram, which was created on the basis of 1,039 patients who underwent R0 resection for gastric adenocarcinoma, both the number of positive LNs, but also the number of negative LNs were found to provide prognostic information for DSS.[21] Taken together, these data demonstrate that (at least in the subset of gastric cancer patients with less advanced stage), a more extensive lymphadenectomy may be associated with prolonged survival. The mechanism for this association is unclear, but could be related to superior locoregional disease control. In other words, in high advanced gastric cancer, the survival does not seem to depend on the loco-regional disease control but possibly other potential factors, such as tumor biology or host immunity.

The sizeable perioperative mortality rates of 10% to 13% of the D2 arm in the Western randomized trials were reported in sharp contrast to the much lower rates described by Asian institutions. [3,5] This difference could be partially explained by the lower incidence of gastric cancer in Western countries (leading perhaps to lesser surgical experience compared with Asia) and the higher incidence of central obesity (increased visceral fat) in Western patients, which poses further technical challenges for an abdominal lymphadenectomy. However, several subsequent Western studies from Italy,[7] Germany,[16] and the US[22] have reported similar perioperative mortality rates between D1 and D2 dissections. These results substantiate our findings showing similar perioperative mortality rates between patients who had 7–15 and more than 16 LNs removed (4.7% versus 3.1%, respectively, Table 1).

The concept that harvesting more LNs is associated with improved survival has been previously reported in other gastrointestinal tract cancers, including colon and esophageal cancer. A secondary survey of the intergroup trial INT-0089 utilized data from 3,322 patients with stage II and III colon cancer to analyze the effect of the number of LNs examined on survival. After controlling for the number of involved LNs, survival significantly increased as more LNs were analyzed.[23] Likewise, a multi-institutional analysis of 2,303 esophageal cancer patients showed that the number of LNs removed during esophagectomy was an independent predictor of survival.[24]

There are several aspects of this analysis that require careful interpretation. First, there are inherent selection biases submerged in any retrospective analysis that are difficult to control for. Patients with more LNs removed may have improved survival simply because they had a better “performance status” and likely to get more aggressive treatment, including more extensive LN dissection. Second, the number of LNs removed does not only reflect the number of LNs dissected intraoperatively, but also the number of LNs identified during pathologic evaluation of the specimen. Although, collaboration between multiple institutions limits the ability to easily standardize surgical and pathologic practices, the multicenter nature of our study is also a strength as it contributes to the generalizability of our findings. Furthermore, the modern study period (2000–2012) and the fact that all participating institutions were academic medical centers in the US contribute to the homogeneity and granularity of our dataset. Last, as previously described, stage migration is a particular challenge for any analysis of this kind. Two *a priori* strategies were used in this direction. We excluded patients with less than 7 LNs removed from the first (univariate) part of our analysis, in order to assure accurate staging of the remaining patients as much as possible. In addition, when performing the second part of our analysis (multivariate analysis of DSS as a function of the number of LNs removed), we did not include the number of positive LNs in the model, but instead incorporated this information into our $\hat{S}$ classification. This classification improves on previous approaches, based just on number of positive LNs or observed ratio, by using both of these quantities to compute the probability of having a true large fraction of positive LNs.

In conclusion, using a contemporary, multi-institutional cohort of gastric adenocarcinoma patients from seven US academic institutions, we found that the number of lymph nodes removed appears to have prognostic implications for survival in all, except advanced stage patients (III-B and III-C or N_3). This survival benefit appeared to plateau beyond the removal of 16 lymph nodes. These findings corroborate recent evidence from prospective randomized trials in favor of extended node dissection during curative resection for gastric cancer. It is difficult to completely separate the impact of improved regional disease control from stage migration as the underlying mechanism for this observation. However, these results call for attention to the number of lymph nodes removed not only as a powerful qualifier of staging accuracy, but also as an important predictor of outcome for patients with gastric cancer. This factor should be included in the stratification of patients for future clinical trials on this disease.

Abbreviations

LN	Lymph nodes
AJCC	American Joint Committee on Cancer
DSS	disease specific survival
SD	standard deviation
HR	hazard ratio
r	ratio of positive to removed LNs

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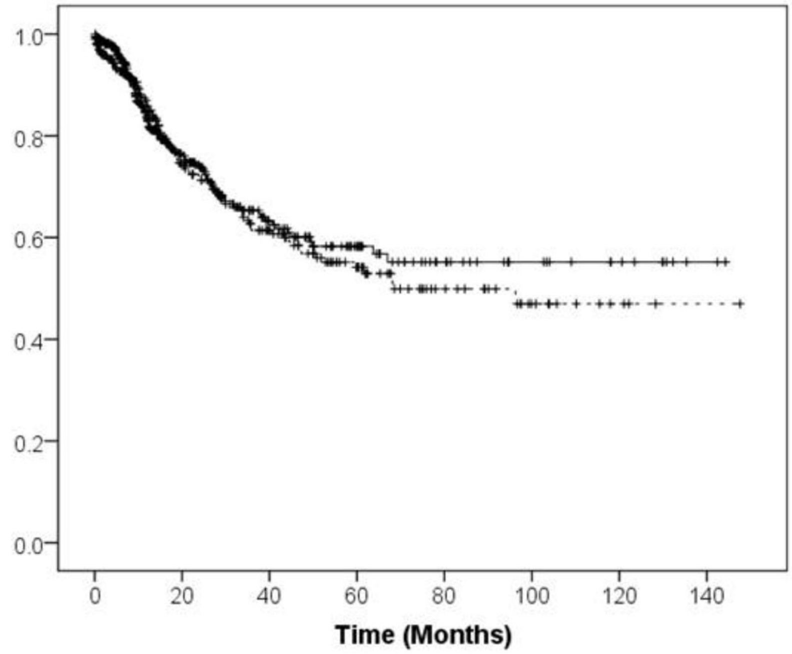

Figure 1.
Disease-specific survival curves for the entire study population based on the number of lymph nodes examined (continuous line: 16 or more lymph nodes, n = 485, 10-year DSS 55%; dashed line: 7–15 lymph nodes, n = 257, 10-year DSS 47%; P = 0.53).

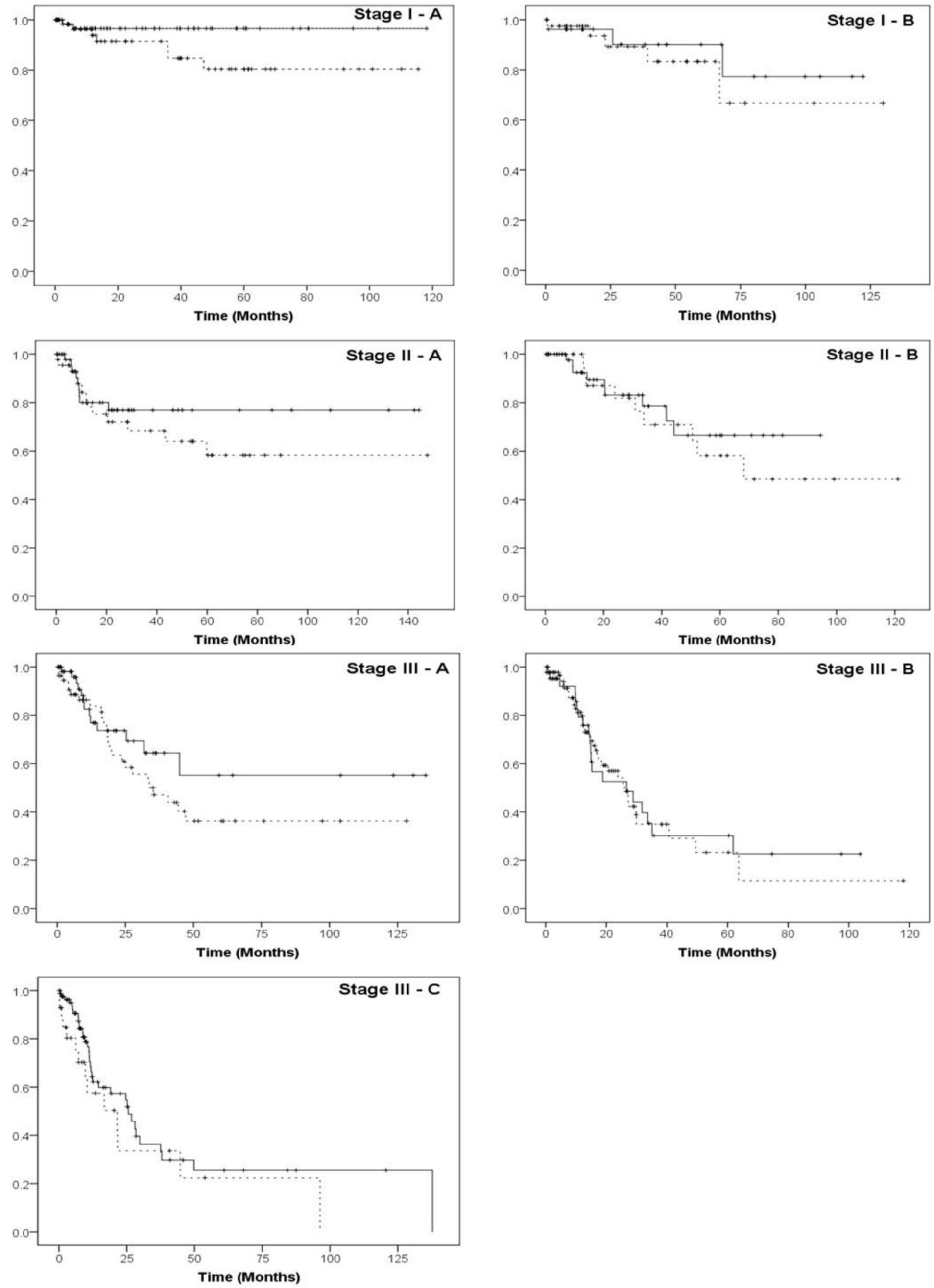

Figure 2.

Subset analysis of disease-specific survival curves after resection of gastric adenocarcinoma stratified by AJCC stage (7th edition). Although P values for all stages were > 0.05, patients who had 16 or more lymph nodes examined (continuous line) tended to have improved survival compared with patients who had 7–15 lymph nodes examined (dashed line) in Stages I-A through III-A, but not in stages III-B and III-C.

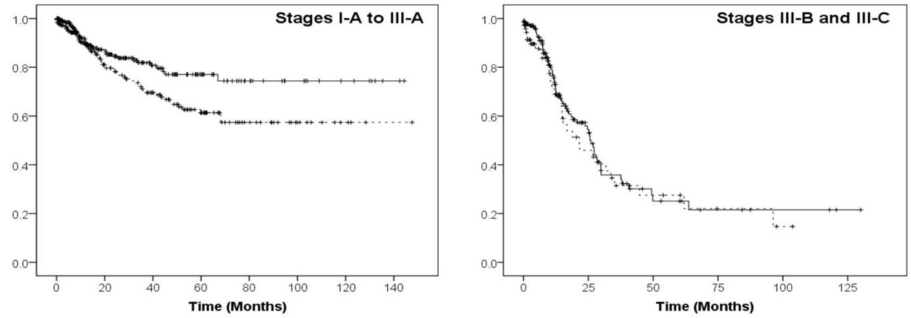

Figure 3.

When stages I-A through III-A were combined together, patients with gastric adenocarcinoma who had 16 or more lymph nodes removed (continuous line, n = 269) had improved outcome after resection compared with patients who had 7–15 lymph nodes examined (dashed line, n = 229) with 10-year disease-specific survival rates of 74% versus 57% respectively (P = 0.018). This difference was not observed when stages III-B and III-C were analyzed together (P = 0.55).

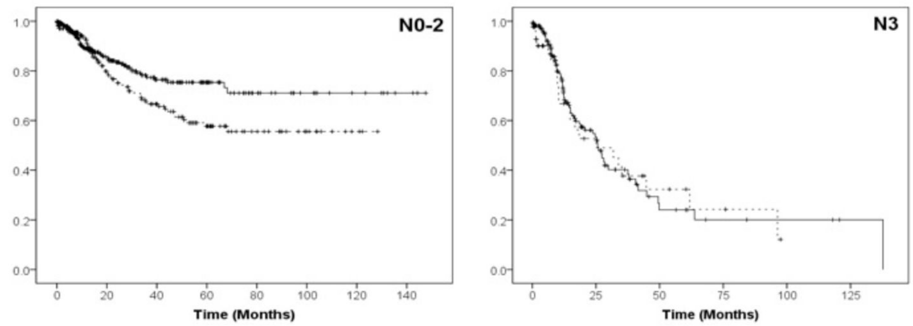

Figure 4.

When stages N_0 through N_2 were combined together, patients with gastric adenocarcinoma who had 16 or more lymph nodes examined (continuous line, n = 315) had improved outcome after resection compared with patients who had 7–15 lymph nodes examined (dashed line, n = 213) with 10-year disease-specific survival rates of 72% versus 55% respectively (P = 0.023). This difference was not observed in patients with N_3 disease (P = 0.882).

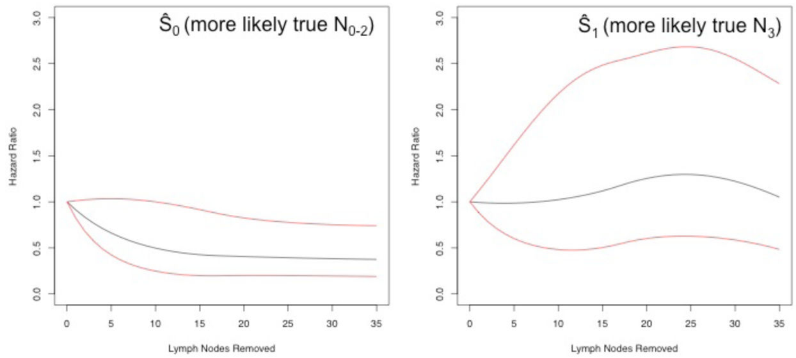

Figure 5.

A Cox proportional hazards model was utilized to compute the Hazard Ratio (HR) for gastric cancer related death (black line, red lines illustrate 95% confidence interval) as a function of the total number of lymph nodes removed (Reference is 0 nodes removed). HR was adjusted for T stage, grade, margin status, receipt neoadjuvant chemotherapy, adjuvant chemotherapy or radiation, and institution. On the left, when less advanced stage patients were analyzed ($\hat{S}_{0,}$ more likely to be true N_{0-2}, n = 676), the HR appears to decrease as the number of removed lymph nodes increases, but there does not appear to be an incremental benefit beyond 16 lymph nodes removed. On the right, when more advanced stage patients were analyzed ($\hat{S}_{1,}$ more likely to be true N_3, n = 163), no significant correlation between the HR and the number of lymph nodes removed was demonstrated.

Table 1

Clinical, pathologic, intraoperative and postoperative variables stratified by number of lymph nodes removed.

	7 – 15 Nodes n = 257	**≥ 16 Nodes n = 485**	**P**
Age (years)	66 (13)	64 (12)	**.018**
Male Gender	157 (61%)	265 (55%)	0.09
White (vs Non-white) Race	162 (63%)	298 (61%)	0.43
ASA score	2.72 (0.61)	2.67 (0.56)	0.26
BMI	25.9 (5.8)	26.2 (6.0)	0.56
Neoadjuvant Chemotherapy	47 (30.3%)	108 (69.7%)	0.33
Adjuvant Chemotherapy/Radiation	112 (29.5%)	267 (70.4%)	0.003
Total (vs Partial) Gastrectomy	94 (37%)	223 (46%)	0.07
D2 (vs D1) Lymphadenectomy	133 (52%)	337 (69%)	**< 0.001**
Splenectomy	18 (7%)	52 (11%)	0.09
Pancreatectomy	9 (3.5%)	31 (6%)	0.12
Operative Time (min)	265 (110)	243 (88)	**0.02**
Estimated Blood Loss (ml)	296 (293)	286 (248)	0.65
Blood Transfusion	58 (23%)	105 (22%)	0.96
Proximal Margin Positive	12 (5%)	40 (8%)	0.14
Distal Margin Positive	5 (2%)	13 (3%)	0.74
Lauren Classification			0.07
Diffuse	45 (17%)	119 (24%)	
Intestinal	116 (45%)	206 (42%)	
Mixed	4 (2%)	3%)	
Unknown	92 (36%)	146 (30%)	
T3 or T4	146 (57%)	317 (65%)	**0.02**
Poor Grade	142 (55%)	295 (61%)	0.16
Nodal Status			**< 0.001**
N0	105 (41%)	159 (33%)	
N1 (1–2 positive nodes)	45 (17.5%)	85 (17%)	
N2 (3–6 positive nodes)	63 (24.5%)	71 (15%)	
N3 (7 or more positive nodes)	44 (17%)	170 (35%)	
Any Postoperative Complication	107 (42%)	212 (44%)	0.58
Clavien-Dindo Grade of Complication			0.16
I	10 (4%)	29 (6%)	
II	51 (20%)	100 (21%)	
III	18 (7%)	41 (8.5)	
IV	13 (5%)	32 (7%)	
Unknown	150 (58%)	271 (56%)	
Length of Stay (Days)	11 (8)	11 (8)	0.82

	7 – 15 Nodes n = 257	≥ 16 Nodes n = 485	P
Readmission	61 (24%)	114 (23%)	0.23
In-hospital Mortality	12 (4.7%)	15 (3.1%)	0.30

Data presented as Mean (SD), and absolute count (%). ASA, American Society of Anesthesiologists; BMI, Body Mass Index

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