
Lymphadenectomy with Optimum of 29 Lymph Nodes Retrieved Associated with Improved Survival in Advanced Gastric Cancer: A 25,000-Patient International Database Study



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- BACKGROUND:** Gastric adenocarcinoma is an aggressive disease with frequent lymph node (LN) metastases for which lymphadenectomy results in a survival benefit. In the US, the National Comprehensive Cancer Network guidelines recommend D2 lymphadenectomy or a minimum of 15 LNs retrieved. However, retrieval of only 15 LNs is considered by most international guidelines as inadequate. We sought to evaluate the survival benefits associated with a more complete lymphadenectomy.
- STUDY DESIGN:** An international database was constructed by combining gastric cancer cases from the Surveillance, Epidemiology, and End Results program database ($n = 13,932$) and the Yonsei University Gastric Cancer database ($n = 11,358$) (total $n = 25,289$). Kaplan-Meier survival analysis was performed along with Joinpoint analysis to obtain the optimal number of LNs to retrieve based on survival. Prognostic significance of number of nodes retrieved was then confirmed with univariate and multivariate analyses.
- RESULTS:** Analysis for both mean and median survival yielded 29 LNs removed as the Joinpoint. This was confirmed with multivariate analysis, where 15 retrieved LNs cutoff fell out of the model and 29 retrieved LNs remained intact, with a hazard ratio of 0.799 (95% CI 0.759 to 0.842; $p < 0.001$). Stage-stratified Kaplan-Meier analysis for a cutoff point of 29 LNs also demonstrated a statistically significant improvement in survival.
- CONCLUSIONS:** Joinpoint analysis has allowed for the creation of a model demonstrating the point at which additional dissection would not provide additional benefit. This large international dataset analysis demonstrates that the maximal survival advantage is seen by performing a lymphadenectomy with a minimum of 29 LNs retrieved. (*J Am Coll Surg* 2017;224:546–555. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)
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Surgical resection remains the primary curative therapy for gastric adenocarcinoma, which is an aggressive disease requiring multimodality treatment. Although survival

benefit of additional chemotherapy has been established (MAGIC [Medical Research Council Adjuvant Gastric Infusional Chemotherapy], McDonald, CLASSIC, ACT trials),^{1–4} the timing and extent of surgical treatment continues to be investigated. As one of the most important determinants of recurrence and long-term survival in patients undergoing radical gastrectomy is nodal metastases, management of nodal disease is a key component to ensuring the best patient outcomes.⁵ Specifically, the proper extent of lymph node (LN) dissection and the specific number of nodes required for adequate staging has generated decades of discourse with variable worldwide practice.^{6,7}

The prognostic importance of nodal positivity is reflected in the 7th edition of the TNM staging system of gastric cancer.⁸ Treatment planning is guided by

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Drs Woo and Goldner contributed equally to this work.

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Abbreviations and Acronyms

AJCC	= American Joint Committee on Cancer
HR	= hazard ratio
LN	= lymph node
NCCN	= National Comprehensive Cancer Network
SEER	= Surveillance, Epidemiology, and End Results

predicted nodal metastases and prognosis guided by the number of pathologically positive LNs and subsequent accurate staging of the disease. In addition, D2 lymphadenectomy, which allows for clearance of the nodal stations likely harboring metastatic disease and increased number of nodes for evaluation, is now internationally accepted as the standard procedure with demonstrated decreased regional recurrence and improved long-term survival for patients undergoing curative surgery.⁹⁻¹³ Many guidelines (Italian Gastric Cancer Study Group, the German Gastric Carcinoma Study Group, the Brazilian Gastric Cancer Association and the Chinese Gastric Cancer Association) support D2 lymphadenectomy as the optimum extent of LN dissection.¹⁴⁻¹⁶ Although D2 LN dissection has long been advocated as the surgical standard for radical gastrectomy in Japan and South Korea by the Japanese Research Society for Gastric Cancer and Korean Gastric Cancer Association,^{17,18} D2 lymphadenectomy in Western studies has until recently been associated with forbidding morbidity and mortality.

In the US, the National Comprehensive Cancer Network (NCCN) Guidelines have adopted D2 lymphadenectomy as the standard surgical treatment, with an additional goal of removing a minimum of 15 LNs.¹⁹ This recommendation was based on a study that identified 15 as the minimal number of LNs retrieved that was associated with a survival benefit. This study and several others have demonstrated that there is a continued incremental increase in survival per stage up to 40 LNs. At present, the oncologic quality of the LN dissection is measured by the removal and evaluation of at least 15 LNs to meet NCCN guidelines for proper staging according to the TNM staging system. Of note, the expected LN count obtained by a D2 lymphadenectomy is generally considerably higher than 15. A study examining mean number of LNs obtained during dissection of cadavers predicted a mean of 31.1 LNs would be retrieved during a D2 LN dissection for a total gastrectomy and 29.1 for a distal gastrectomy.²⁰ Results of many clinical trials in which data for D2 LN numbers are available indicate that an adequate nodal dissection for D2 would yield at least 33 to 47 LNs.^{10,21,22}

Our study aimed to define the optimum number of LNs needed to be retrieved during radical gastrectomy for maximum survival benefit using the largest combined international dataset created to date.

METHODS

To develop an international dataset with both Western and East Asian gastric cancer patients, data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database²³ and combined with data from Yonsei University, Seoul, Korea. The following factors were obtained from the data: age, sex, ethnicity, histology, surgery performed, T-classification, N-classification, M-classification, stage, total number of LNs examined, and total number of positive LNs, vital status, and survival. The Yonsei University gastric cancer database is prospectively maintained and all information was pulled directly from the database after meticulous verification through internal quality-control measures. All staging data within the database were updated and coded to confirm to the American Joint Committee on Cancer (AJCC) TNM 7th edition staging system.

Due to changes in coding, specifically AJCC TNM staging, only the years 2002 to 2012 were extracted for use from the SEER database. The SEER database was searched, identifying ICD-0-3 site recode for "stomach" and then further narrowed down using the behavior code "malignant," initially obtaining 57,237 potentially patients. The ICD-0-3 histology/behavior codes were then used to identify only the cases of gastric adenocarcinoma, eliminating other gastric tumors (neuroendocrine, gastrointestinal stromal tumor, unknown, metastatic disease). We then obtained data from the following categories: "sex," "age recode with single ages and 85+," "grade," "icd-o-3 hist/behav," "derived ajcc t, 6th ed (2004+)," "derived ajcc t, 7th ed (2010+)," "derived ajcc m, 6th ed (2004+)," "derived ajcc m, 7th ed (2010+)," "rx sum-surg prim site (1998+)," "regional nodes examined (1988+)," "regional nodes positive (1988+)," "vital status recode (study cutoff used)," "survival months."

All patients with incomplete or unknown information contained within the data were eliminated from the dataset. All patients with stage IV disease were also removed from the dataset. Data on age, sex, nodes examined, nodes positive, vital status, and survival were taken directly from the original data with no need for additional recoding. Histology data were obtained from "grade" and "icd-o-3 hist/behav" and recoded to be: adenocarcinoma well differentiated, adenocarcinoma moderately differentiated, adenocarcinoma poorly differentiated, mucinous

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