Human Pathology (2018) **75**, 55–62

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Regional lymph node sampling in lung carcinoma: a single institutional and national database comparison☆

Dustin E. Bosch MD, PhD[a], Farhood Farjah MD[b], Douglas E. Wood MD, FACS, FRCSEd[b], Rodney A. Schmidt MD, PhD[a,*]

[a]*Department of Pathology, University of Washington, Seattle, WA 98195, USA*
[b]*Department of Surgery, Division of Cardiothoracic Surgery, University of Washington, Seattle, WA 98195, USA*

Received 20 October 2017; revised 31 January 2018; accepted 2 February 2018

Keywords:
Lung carcinoma;
Regional lymph nodes;
Quality metrics;
Cancer staging;
National cancer database

Summary Assessing regional lymph node metastasis is a key component of lung carcinoma staging and prognostication. Recent guidelines have suggested a quality metric of 10 total regional lymph nodes sampled with each stage I-II primary lung carcinoma resection. However, the extent of mediastinal lymph node sampling remains controversial. We assessed factors contributing to regional lymph node counts and effect on overall patient survival in an institutional cohort of 888 cases and the Surveillance, Epidemiology, and End Results national cancer registry (10 856 cases). The distribution of total lymph node counts in lobectomy and pneumonectomy cases was variable with a median of 10 and an interquartile range of 7 to 14. Multiple clinical and pathologic factors correlated with total regional node counts. Total lymph node counts of at least 10 in the institutional cohort did not correlate with significant differences in overall survival as compared with node counts of less than 10 ($P = .38$). In the Surveillance, Epidemiology, and End Results database, although 0 regional lymph nodes were correlated with reduced overall survival (hazard ratio, 1.47; $P < .01$), no significant difference was detected for 1 to 9 versus at least 10 nodes ($P = .8$). In conclusion, lymph node counts for primary lung carcinoma are driven by surgical, pathologic, and biologic variability. We find no evidence for a meaningful quality metric of 10 total regional lymph nodes at the institutional and national registry levels.

1. Introduction

Regional lymph node metastasis in patients with lung cancer is a major determinant of prognosis and has important implications for therapeutic decision making [1]. Standard practice for staging carcinoma in patients undergoing primary resection includes sampling of hilar and mediastinal lymph nodes, as part of the same procedure and/or separate mediastinoscopy or transbronchial biopsy procedures [2]. However, the appropriate extent of regional lymph node sampling and its relationship to patient outcomes has been an area of controversy [3-5]. Retrospective studies of national and state cancer registry data have implicated total regional lymph node counts as significant correlates with patient survival in cases of early stage non–small cell carcinoma [6-8]. When survival was analyzed upon categorizing cases by total regional lymph nodes,

Abbreviations: UW, University of Washington; SEER, Surveillance Epidemiology and End Results.

☆ Disclosures: None.

* Corresponding author at: 1959 NE Pacific St, Box 357470, Seattle, WA 98195.
E-mail address: schmidtr@uw.edu (R. A. Schmidt).

https://doi.org/10.1016/j.humpath.2018.02.002
0046-8177/

significant survival benefits were demonstrated for cases with more lymph nodes than for the reference group (define as 0 nodes in 2 studies and 1-4 nodes in 1 study). However, significant differences between groups with higher total regional lymph nodes (eg, 6-10 versus 11-15) were not reported [6-8]. Prospective studies are fewer, although a randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy in early stage non–small cell lung carcinoma (ACOSOG Z0030 trial) did not reveal a significant difference in survival [9]. A systematic review of similar trials comparing sampling and systematic lymphadenectomy found disagreement among 5 randomized trials [10].

In 2014, the American College of Surgeons Commission on Cancer published a proposed quality metric (10RLN) requiring at least 10 regional lymph nodes to be removed in stage I and II non–small cell lung carcinoma resections [3,4]. As a result, a number of affiliated hospitals within our health system have begun discussion of implementing a minimum total regional lymph node count of 10 as a quality metric for primary lung carcinoma resections. We sought to define the distribution of hilar and mediastinal lymph node sampling at our institution (where there has been a consistent surgical approach throughout the study period) and in a national cancer registry, and reexamine the evidence for a minimum 10 regional lymph nodes as a predictor of patient outcomes.

2. Materials and methods

2.1. Case selection

Lung carcinoma resection cases were identified in the UW pathology database (PowerPath). Pathologic data were extracted from pathology reports (2007–2017) containing a mandatory institutional standardized form (cancer synoptic worksheet) that summarizes staging and prognostic information. The synoptic worksheet for lung carcinoma includes a requirement for entering hilar and mediastinal lymph node counts (N1, N2, and N3) and provides instructions to the pathologist on a standardized approach to counting lymph nodes. Inclusion criteria were adult patients, lung primary neoplasm, carcinoma, and primary resection (including wedge resection, segmentectomy, lobectomy, and pneumonectomy) performed and pathology reviewed at UW. Exclusion criteria were resections for metastatic disease, resections performed at another institution (slide reviews and consults), nonepithelial neoplasms, and biopsies. Cases were defined by the completion of a primary lung carcinoma worksheet, and 29 of the 888 cases were worksheets from patients with multiple lung primary carcinomas. Cases were designated as having prior invasive mediastinal staging (mediastinoscopy and/or endobronchial or esophageal ultrasound-guided nodal aspiration) if a separate lymph node specimen from the same patient was evaluated at UW within 120 days of primary resection.

At our institution, surgeons submitted node fragments from mediastinoscopic procedures in separate specimen containers for each node and pathologists counted each specimen as a single lymph node. Intact lymph nodes from open mediastinal sampling or pathologic specimen dissection were inked and counted individually by the pathologists. Thus, we expect the number of N2 + N3 lymph nodes counted to be equal to or slightly in excess of the number lymph node specimens submitted (the excess being where multiple nodes were submitted in a single open mediastinal station specimen).

Compliance with the institutional standard of counting lymph nodes was assessed by reviewing the pathology reports of 180 cases with the largest number of mediastinal lymph nodes and excluding potentially noncompliant cases. In addition, total lymph node specimen counts were compared with the N2 and N3 lymph node counts. Cases with N2 + N3 lymph node counts greater than the total specimen count were identified as potentially noncompliant.

Institutional cancer registry data were extracted from pathology reports of the primary resection. Mediastinal lymph node sampling performed in separate procedures and/or at outside institutions was not uniformly incorporated into the registry lymph node count entered into the registry. With institutional review board protocol approval, lung carcinoma resection cases were linked with institutional cancer registry survival data. All-cause mortality was defined as time from primary resection to death or last contact (censored).

National lung carcinoma resection data were gathered from the SEER Program (www.seer.cancer.gov) Research Data (1973-2014), National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, released April 2017, based on the November 2016 submission. Inclusion criteria included lung primary site, carcinoma diagnosis, and primary resection (including wedge resection, segmentectomy, major airway resection, lobectomy, and pneumonectomy). Exclusion criteria included metastatic disease, nonepithelial neoplasms, and biopsies. For survival analyses, cases with low stage, pT1, or pT2 with no nodal or distant metastases at the time of surgery were selected. Cases lacking any of the following were excluded from the survival analysis: T stage, N stage, regional lymph node count, or survival time.

2.2. Statistics

Associations of mediastinal lymph node counts and pN stage were assessed using a nonparametric Kruskal–Wallis log-rank test. A P value less than .05 was considered sufficient to reject the null hypothesis. All-cause mortality was assessed with Kaplan-Meier curves and Cox regression modeling [11] to derive hazard ratios for continuous variables, while log-rank testing (Mantel-Cox) was used to derive χ^2 statistics for categorical variables. A P value less than .05 was considered sufficient to reject the null hypothesis. All statistical calculations were performed with SAS software (SAS University Edition 2; Cary, NC) or Prism 7 (GraphPad, La Jolla, CA), and graphical representations were created with Prism.