An analysis, systematic review, and meta-analysis of the perioperative mortality after neoadjuvant therapy and pneumonectomy for non–small cell lung cancer

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Objective: Pneumonectomy after neoadjuvant therapy remains controversial.

Methods: A systematic PubMed search was performed for original articles from 1990 through 2010 describing pneumonectomy after neoadjuvant therapy. Specific data on 30-day and 90-day perioperative mortalities were abstracted from these articles. Meta-analysis compared 30-day mortality between right and left pneumonectomy with a fixed-effects model. Comparison between 30-day and 90-day mortalities was also performed.

Results: The search strategy yielded 27 studies. Overall, 30-day and 90-day perioperative mortalities were 7% and 12%, respectively. Among 15 studies providing side-specific 30-day mortality, cumulative mortalities were 11% and 5% for right and left pneumonectomies, respectively. In the meta-analysis that included 10 studies, 30-day mortality for right pneumonectomy remained greater than for left pneumonectomy (odds ratio, 1.97; 95% confidence interval, 1.11–3.49; $P = .02$). Among 6 studies providing side-specific 90-day mortality, cumulative mortalities were 20% and 9% for right and left pneumonectomies, respectively. In the meta-analysis that included 4 studies, 90-day mortality for right pneumonectomy was greater than for left pneumonectomy (odds ratio, 2.01; 95% confidence interval, 1.09–3.72; $P = .03$). Among 11 studies providing both 30-day and 90-day mortalities, mortality difference was 5% (95% confidence interval, 4%–7%, $P < .0001$). Pulmonary complications were the most common cause of 30-day and 90-day deaths.

Conclusions: Right pneumonectomy is associated with significantly higher 30-day and 90-day mortalities after neoadjuvant therapy than left pneumonectomy. Also, 90-day mortality for all pneumonectomies appears to be greater than expected, suggesting that the 30-day mortality figure may inadequately assess the perioperative mortality. (J Thorac Cardiovasc Surg 2012;143:55-63)

Pneumonectomy has been associated with increased morbidity and mortality relative to other pulmonary resections.[1] In particular, the mortality for pneumonectomy after neoadjuvant therapy has been thought by some to be prohibitively high.[2] Reports with alarmingly high mortality (>20%), however, have been countered by other reports with very low mortality (<5%). This leaves unclear the correct approach for a patient with preoperatively identified N2 disease who would need a pneumonectomy. Often, this situation involves a large central tumor, which may limit the dose of radiotherapy that can be safely given, also making the alternative of definitive chemoradiation less appealing. Particularly for young patients, in whom the risk of surgical mortality in general is low, it is unclear whether the mortality after neoadjuvant therapy and pneumonectomy is in fact low enough to justify this approach.

The main hypothesis is that the published literature does not support the notion that all pneumonectomies after neoadjuvant therapy are categorically associated with high perioperative mortalities. The primary objective was to demonstrate that right pneumonectomy and not left pneumonectomy in particular is associated with a significantly higher perioperative mortality. The secondary objectives of this review were (1) to determine whether 30-day mortality is different from 90-day mortality and (2) to determine which perioperative complications contribute to perioperative mortality.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines were followed as closely as possible for this systematic review. At the time of the writing of this article, there was no known review protocol specific to the objectives outlined previously.

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Abbreviation and Acronym
PRISMA = Preferred Reporting Items for Systematic reviews and Meta-analysis

Search Strategy

A comprehensive English-language literature search was performed with the PubMed database to identify published articles (including articles in press and those published exclusively electronically) reporting pulmonary resections after neoadjuvant chemotherapy or chemoradiation therapy between January 1, 1990, and April 30, 2010. A Boolean search strategy was used with the search terms "non–small cell lung cancer" and "pneumonectomy," "induction," and "neoadjuvant." Publications were included if they met the following criteria: (1) they included more than 20 patients who underwent pneumonectomy after neoadjuvant chemotherapy or chemoradiation therapy, (2) they reported the indication for resection was non–small cell lung cancer, and (3) they reported specific perioperative mortality. Publications were excluded for any of the following reasons: (1) central focus of the study on carinal or sleeve pneumonectomy, (2) central focus of the study on extrapleural pneumonectomy, (3) indication for pneumonectomy for disease processes other than non–small cell lung cancer (eg, mesothelioma, small cell lung cancer, or metastatic disease), (4) not more than 20 pneumonectomies, or (5) lack of pneumonectomy-specific data, particularly resection-specific perioperative mortality. Extended pneumonectomies (eg, with pericardial, great vessel, or chest wall resection) were included as long as they did not include carinal or sleeve pneumonectomies. The search further excluded case reports and reviews. Studies from authors or institutions that reported a series that expanded on an earlier series were included; however, the earlier series were not included in these cases. Studies were not excluded on the basis of the type of chemotherapy or chemoradiation therapy regimens that were used.

Data Abstracted

Specific data that were collected included the period of time in which the patients were either accrued or studied, number of institutions, method of staging, percentage of patients with stage III disease, and the use of neoadjuvant chemotherapy or chemoradiation therapy, including the regimens and doses. The total number of pneumonectomies, the overall 30-day and 90-day mortalities, and the distributions according to the laterality of resection (when available) were also recorded. In the analysis for this review, the 30-day mortality figures actually reflected publications that reported mortality with a specific 30-day period and those reported as any in-hospital mortality. We were not able to separate further in-hospital mortality from 30-day mortality, because that information generally was not provided.

All the articles included in this study were thoroughly reviewed, and the mortalities included reflect either explicit mortality figures that were reported, mortality figures that were calculated from the information provided in the articles not explicitly reporting mortality, or mortality figures abstracted from the discussion of the article if mortality was presented at a meeting but not listed in the original article. If the mortality was neither provided nor calculable on the basis of the existing information, it could not be factored into the analysis. Each article was reviewed several times to ensure that data were neither missed nor erroneously labeled.

Complications that caused or contributed to perioperative mortality were also abstracted and analyzed. The incidence of complications in general was not included, because the definitions and diligence of reporting were highly variable. Complications associated with perioperative death were grouped into 4 broad categories: pulmonary, infectious, cardiac, and other. Pulmonary complications were those complications that included pneumonia, acute respiratory distress syndrome, and atelectasis requiring bronchoscopic intervention. The infectious category comprised bronchopleural fistula and empyema complications. Pneumonia was grouped with pulmonary complications primarily because this is how it was reported in many of the articles. Furthermore, distinguishing actual pneumonia from acute respiratory distress syndrome was not always possible because the distinction was not immediately clear, and often antibiotics are given empirically for patients with acute respiratory distress syndrome. Cardiac complications consisted of cardiac arrhythmias, heart failure, myocardial infarction, and other cardiac issues. The "other" complications included gastrointestinal complications, recurrent laryngeal nerve injury, bleeding or hemothorax, wound issues, and a variety of other nonspecific issues. Venous thromboembolic complications, including pulmonary embolism, were also grouped in this category.

Assessments of Study Quality and Publication Bias

Because quality scoring in any systematic review or meta-analysis for observational studies is controversial,[3-5] an internally developed 6-point criteria system was developed to assess quality. The criteria selected were based on clinical factors believed to be associated with improved outcomes and consisted of data that were consistently identifiable as being included or not included in each study. These criteria included the following: size of study, duration of study, era of study, performance in a multicenter paradigm, inclusion of more than half of the patients with stage III disease, and the use of invasive staging. The median duration in years (<8 years or ≥ 8 years) was used to determine whether the study was long or not long. Studies published after and including 1994 or before 1994 were considered later or earlier studies, respectively. The median number of patients included among all the studies (<68 or ≥ 68) was used to dichotomize studies as large or not large. The numbers of institutions involved were grouped into 1 versus more than 1, on the basis of speculation that this difference would be more revealing than a threshold of a given number of multiple institutions (eg, 4 vs ≥ 5). Performance of invasive mediastinal staging routinely in all of the patients versus in some or an unknown number of patients was used to dichotomize the studies.

To be considered highest quality or high quality, at least 4 or 2, respectively, of the 6 criteria had to be met. Any study with no criteria or 1 criterion was considered to be low quality and was excluded from the analysis. Subgroup analyses of 30-day mortality between highest-quality and high-quality studies were performed. If a significant difference was found between highest-quality and high-quality studies, then the Woolf method (inverse variance method) was used for a fixed-effects analysis and the DerSimonian-Laird method was used for a random-effects analysis. The selected studies were further categorized according to the design of the study, and the subset analyses were performed within each design type. The test of heterogeneity in results across studies was carried out with Higgins I^2, which measures the percentage of total variation across the studies. Publication bias was assessed with Begg funnel plots and Egger tests. If the funnel plot was asymmetric or the P value was less than .05 by Egger test, then a publication bias was assigned.

Statistical Analysis of 30-Day Perioperative Mortality

The pneumonectomy-specific data were analyzed by a meta-analysis that used a fixed-effects model to compare the 30-day mortality figures between left and right pneumonectomies and to compare 30-day and 90-day mortalities. Statistical analysis was performed with the statistical package R, version 2.10.1.[6]

Study Control

There was no formal funding source for this study. We as the authors had complete control of the search, data analysis, and writing. No other individuals were involved.