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)
Pulmonary complications were those complications that were grouped into 4 broad categories: pulmonary, infectious, cardiac, and "other." 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, and (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. 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 were also recorded. 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, 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.

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.
RESULTS

Results of Search

The search strategy identified 315 articles (Figure 1). The individual articles were selected on the basis of year of publication but without regard to the dates of the operations described in the methods and results sections. After screening of the titles and, when appropriate, the abstracts or actual articles, 40 articles were selected for full review. Nine studies were excluded because neither 30-day nor 90-day pneumonectomy-specific mortality was reported.7–15 Of the remaining 31 articles, that matched the selection criteria, 3 additional studies were excluded because of their redundant nature. The patients in 1 study16 were also included in a later article involving a substantially greater number of pneumonectomies. Two other articles17,18 were excluded for redundancy because they reported previously published work and were not as comprehensive in the desired data as the original articles.19,20 One included study21 involved a few sleeve pneumonectomies that could not be separated from the data reported; however, this article was still included in the analysis because of the relatively small number of sleeve pneumonectomies,8 which represented 10% of the pneumonectomies performed in that study. There was 1 article that included only 90-day mortality.22

Ultimately, there were 27 articles that were used for the analysis (Table 1). Of these 27 articles, 7 were prospective studies2,19,23–27 and 20 were retrospective studies.15,16,20–22,28–44 Of the 7 prospective trials, 4 were randomized controlled trials2,19,24,27 and 3 were cohort studies.23,25,26 Of the 20 retrospective studies, 8 were cohort studies39–40,42–45 and 12 were descriptive studies.16,18,20,28–30,32–34,36–38,41,46

Study Quality

The 27 studies selected for this review were grouped into 3 subgroups: randomized controlled trials (prospective), cohort studies (prospective and retrospective), and descriptive studies (retrospective). Within these subgroups, the quality of each study was graded on the investigator-derived 6-point scoring system (Table 2). As would be expected, 3 of the 4 randomized controlled trials were of the highest quality. Among the cohort and descriptive studies, there were 1 of 11 and 2 of 12 studies that were of the highest quality, respectively. Study quality did not significantly affect either the 30-day mortality or the 90-day mortality.

Publication Bias and Heterogeneity

Funnel plots generated for each of the subgroups demonstrated that there was no significant publication bias among studies reporting increased 30-day and 90-day mortalities for right-sided relative to left-sided pneumonectomy or increased 90-day mortality relative to 30-day mortality (Figure 2). There were 15 studies reporting side-specific 30-day mortality, with 5 being excluded from the 30-day funnel plots. There were 6 studies
reporting side-specific 90-day mortality, with 2 being excluded from the 90-day mortality funnel plots. The studies were excluded because either the total mortality, the right-sided mortality, or the left-sided mortality was 0%. In these studies, the individual odds ratio and variance for each study would both be infinity. In the meta-analysis, the weight associated with each study was 0, and these studies therefore would not contribute to the final estimate of odds ratio. The test for heterogeneity demonstrated that there was no substantial heterogeneity among the groups and subgroups when evaluated in terms of 30-day and 90-day mortalities for right versus left pneumonectomy or increased 90-day mortality relative to 30-day mortality.

**Right Versus Left Pneumonectomy**

**Perioperative mortality at 30 days.** The overall 30-day mortality among the 27 studies was 7% (Table 2). Among the 15 studies reporting side-specific 30-day mortality, the cumulative mortalities were 11% and 5% for right and left pneumonectomies, respectively (Figure 3). In the meta-analysis of 10 studies, the odds ratio of the 30-day mortality (right vs left pneumonectomy) was 2.01 (95% confidence interval, 1.09–3.49). This effect was statistically significant ($P = .02$). No significant heterogeneity results were found ($I^2 = 0.7\%$).

**Perioperative mortality at 90 days.** The overall 90-day mortality among the 27 studies was 12%. Among the 6 studies reporting side-specific 90-day mortality, the cumulative mortalities were 20% and 9% for right and left pneumonectomies, respectively (Figure 3). In the meta-analysis of 4 studies, the odds ratio for 90-day mortality for right pneumonectomy vs left pneumonectomy was 1.97 (95% confidence interval, 1.11–3.49). This effect was statistically significant ($P = .02$). No significant heterogeneity results were found ($I^2 = 0.7\%$).
Difference Between 30-Day and 90-Day Perioperative Mortalities

Both 30-day and 90-day mortality data were reported in 11 studies; the other 16 provided only one set of data or the other. These 11 studies were thought to provide a more accurate comparison of 30 and 90-day mortalities (Table 3). From these 11 studies, the 90-day mortality was apparently significantly higher than the 30-day mortality (difference, 5\%\(^{2}^{2}\); 95\% confidence interval, 4.0\%–6.8\%; \(P < .0001, I^{2} = 0\)). Among these studies, increases from 30-day to 90-day mortality were statistically significant on both the right side (9\%; \(P = .0001\)) and the left side (7\%; \(P = .001\)).

Effect of Radiation Therapy

The use of radiation therapy was not associated with any increases in 30-day or 90-day mortality. A lack of any significant findings was observed when comparing studies that routinely used radiation with those that either used it sometimes or never described its use, as well as when the latter 2 groups were combined (routinely vs sometimes and never).

Causes of Perioperative Mortality

Information regarding cause of 30-day mortality after pneumonectomy after neoadjuvant therapy were provided in 11 studies (1 prospective\(^{2}^{2}\) and 10 retrospective\(^{16,30-32,34,35,37,41,44,47}\)). Half of the perioperative deaths were caused by a pulmonary complication (Figure 4), with the other categories divided approximately equally. There were only 7 studies that reported details of the causes of 90-day mortality.\(^{16,22,26,29,32,37,38}\) Pulmonary complications still accounted for the most
deaths (40%), but there were also more in the “other” category. In addition, there were more infections complications as a cause of 90-day mortality than of 30-day mortality (24% vs 14%; \( P = .012 \)).

**DISCUSSION**

**Impact of Laterality of Resection**

A specific focus of this review was exploring the answer to the question of whether a right pneumonectomy after neoadjuvant therapy justified or to be avoided. The Intergroup 0139 trial\(^2\) promoted concern about right pneumonectomy, because an (unplanned) subgroup analysis suggested that the observed 38% 30-day mortality more than offset any benefit that might have resulted from adding surgery to the therapeutic strategy. The results of this meta-analysis suggest that right pneumonectomy is, in fact, associated with an increased risk of perioperative mortality. This study was not one in which the risk factors for perioperative death associated with neoadjuvant therapy and pneumonectomy were examined, however, and it is therefore impossible to know the actual reason for this increased risk.

It appears that a left pneumonectomy after neoadjuvant therapy can be justified from the standpoint of either 30- or 90-day mortality. Of course, the patients must be assessed for suitability for surgery, and it remains controversial whether surgery should be included in the treatment strategy for patients with N2 node involvement.

On the other hand, whether a right pneumonectomy is wise is less clear. It appears to be well justified on the basis of the 30-day mortality, and also of the experience of some institutions. The 90-day mortality is probably a better outcome measure, however, and the overall 20% average mortality raises concern. Perhaps the conclusion should be that patients should be selected very carefully for this approach and that it should be done primarily in centers with sufficient experience and with a documented low mortality for right pneumonectomy after neoadjuvant therapy. The data clearly demonstrate a strong correlation between pneumonectomy mortality and center volume, as well as surgeon specialization and a focus on noncardiac thoracic surgery.\(^48,49\)

**Difference in 30-Day and 90-Day Mortalities**

What is the best measure of perioperative mortality? Traditionally, 30-day or in-hospital mortality has been chosen. Most studies now, however, report only 30-day mortality. It is easier to identify the dates of surgery and of death...
than to verify that the patient was continually hospitalized. It may also be true that at one time most deaths related to a surgical procedure occurred within 30 days. With better intensive care unit care and methods of life support, however, this may be changing. We found that 90-day mortality appears to be a better measure to use, because it more accurately captures the impact of the surgical procedure. This is particularly true for right pneumonectomy, because the increase between 30 and 90 days was not so large for the left side.

We found that the reported 30-day mortality for a pneumonectomy after neoadjuvant therapy was similar to that reported for pneumonectomy in general.\(^1,51\) This is corroborated by other studies that have compared mortality of pneumonectomy with or without neoadjuvant therapy, which have also found no difference.\(^{15,35,39,40,42-44,52}\) Much of pneumonectomy with or without neoadjuvant therapy, corroborated by other studies that have compared mortality after neoadjuvant therapy was similar to that reported for pneumonectomy in general.\(^1,51\) This is particularly true for right pneumonectomy, because the increase between 30 and 90 days was not so large for the left side.

The mortality at 90 days is significantly higher than at 30 days in our review. Doddoli and colleagues\(^16\) suggested that the 90-day mortality was a more accurate reflection of the mortality associated with pneumonectomy after neoadjuvant therapy. Although the 90-day mortality can naturally be expected to be higher than the 30-day mortality, it is rather surprising that the rate increased as substantially as it did, especially for right pneumonectomy. It is not clear whether the increase is because of neoadjuvant therapy, because of changes in cardiopulmonary function after pneumonectomy, or because it takes longer for complications to lead to actual death.\(^{35-55}\)

### TABLE 3. Summary of 90-day mortality associated with pneumonectomy after neoadjuvant therapy from the studies that provided both 30-day and 90-day mortalities

<table>
<thead>
<tr>
<th>Authors</th>
<th>Total 90-d mortality (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Prospective randomized controlled trials</td>
<td></td>
</tr>
<tr>
<td>Van Schil(^{17,19})</td>
<td>8/69 (11%)</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>1/34 (3%)</td>
</tr>
<tr>
<td>Pezzetta(^{26})</td>
<td></td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td></td>
</tr>
<tr>
<td>Mansour(^{30})</td>
<td>7/60 (12%)</td>
</tr>
<tr>
<td>Refai(^{43})</td>
<td>12/102 (12%)</td>
</tr>
<tr>
<td>Descriptive</td>
<td></td>
</tr>
<tr>
<td>Kim(^{32})</td>
<td>19/129 (15%)</td>
</tr>
<tr>
<td>Doddoli(^{16,46})</td>
<td>21/100 (21%)</td>
</tr>
<tr>
<td>Thibout(^{29})</td>
<td>21/228 (9%)</td>
</tr>
<tr>
<td>Martin(^{8,20})</td>
<td>11/97 (11%)</td>
</tr>
<tr>
<td>Krasna(^{38})</td>
<td>2/29 (7%)</td>
</tr>
<tr>
<td>Allen(^{37})</td>
<td>7/73 (10%)</td>
</tr>
<tr>
<td>Alifano(^{41})</td>
<td>13/118 (11%)</td>
</tr>
<tr>
<td>Average</td>
<td>122/1039 (12%)</td>
</tr>
</tbody>
</table>

\(^{*}\)Unknown laterality of 1 patient. \(^{†}\)Total number from which analysis performed was 77.

Morbidities and Their Sequelae

Pulmonary complications were the most common cause of death among patients undergoing neoadjuvant therapy and pneumonectomy. It is surprising that infectious complications were not a more common cause of death, in light of the frequent concern of bronchopleural fistula as a cause of death after pneumonectomy.

Limitations

A limitation of this review is that multiple investigators did not search and select the studies. Nevertheless, throughout the review process, exhaustive ancillary searches were performed to ensure that no studies were erroneously excluded. Another limitation of this review is that the chemotherapy regimens used among the different studies incorporated in this analysis were fairly diverse. These consistently involved platinum-based therapy, but there was variability in the second or third agent. This may have accounted for the higher incidence of complications in some studies, but this was not able to be analyzed. Additionally, the use of adjuvant therapies was not consistently reported, thus making it difficult to assess the impact of this factor. Another limitation is that no distinction could be made between a simple and a complex pneumonectomy. The increased complexity associated with an intrapericardial pneumonectomy could have contributed to some of the morbidity and
quite possibly to the perioperative mortality that was observed.

CONCLUSIONS

Several conclusions can be drawn from our analysis. When the perioperative period is extended to 90 days, however, the mortality appears to increase substantially (nearly 2-fold). In the setting of obtaining informed consent, an explanation of the elevated risk associated with right pneumonectomy should be discussed. Pulmonary complications appear to contribute the most to perioperative mortality. The incidence of infectious complications appears to have a greater impact on 30-day mortality than on 90-day mortality. Regarding whether a pneumonectomy should be undertaken as part of the treatment strategy after neoadjuvant therapy, the answer appears to be, “It depends.” It appears that in general this approach is justified for a left pneumonectomy; however, the mortality is high enough for a right pneumonectomy that resection must be considered carefully.

References


