COUNTERPOINT: Pneumonectomy after chemoradiation: The risks of trimodality therapy

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Objective: Chemoradiation followed by resection has been studied with increasing interest. Recent publications have stressed the negative side effects of this approach when associated with a pneumonectomy. Right-sided pneumonectomy is associated with a prohibitive mortality rate after preoperative chemoradiation. The article by Boffa and colleagues proposes that this procedure can be performed with relative safety.

Methods: A review of the English literature over 5 years was undertaken to identify articles and presentations involving pneumonectomy after preoperative chemoradiation with curative intent.

Results: Eleven articles reporting results of chemoradiation followed by surgery are reviewed with attention particularly made to results of pneumonectomy. The data from these articles, including morbidity and mortality, are presented. This counterpoint purports to describe the current state of the literature surveyed related to pneumonectomy after chemoradiation.

Conclusion: The majority of articles reviewed stress the high risks of morbidity and mortality with pneumonectomy after chemoradiation. Although some centers still routinely perform this approach, results from prospectively collected data in a careful trial setting are needed to validate this approach. Until then, pneumonectomy after chemoradiation should be used with caution in experienced centers.

Chemoradiation therapy (CRT) followed by resection has been studied with increasing interest in the United States and abroad. Recent publications have stressed the negative side effects of this approach when associated with a pneumonectomy. Specifically, there are numerous studies showing, in particular, that right-sided pneumonectomy is associated with a prohibitive mortality rate after preoperative CRT. This has led some authors to advocate chemotherapy induction alone followed by resection or even deny potentially curative resection in these patients when a pneumonectomy is indicated. The presentation by Boffa and colleagues¹ proposes that this procedure can be performed with relative safety. I have been given the assignment to challenge Boffa and colleagues' proposal that pneumonectomy after neoadjuvant CRT is safe. This counterpoint purports to describe the current state of the literature surveyed related to pneumonectomy after CRT.

MATERIALS AND METHODS

A review of the English literature over the last 5 years was undertaken to identify articles and presentations involving pneumonectomy after preoperative CRT with curative intent. Only articles that discussed separate results of pneumonectomy were included. Key words included *pneumonectomy*,

chemotherapy, radiation therapy, chemoradiation, trimodality therapy, lung cancer, and induction therapy. Case reports were not included in the review.

RESULTS

Eleven abstracts and articles were identified in addition to the article presented by Boffa and colleagues.¹ The role of muscle flap in preventing early and late stump insufficiency was analyzed in patients who underwent extrapleural pneumonectomy for malignant pleural mesothelioma in a series by Beshay and colleagues.² Thirty patients suitable for surgery underwent neoadjuvant chemotherapy using cisplatin and gemcitabine, followed by extrapleural pneumonectomy and 54 Gy of radiotherapy (XRT); 88% of the patients were male with a median age of 65 years. Extrapleural pneumonectomy with muscle flap was performed through an anterolateral thoracotomy. One patient (3%) died of pulmonary embolism on postoperative day 2. Minor complications occurred in the early postoperative phase in 8 patients (25%). There was no early or late bronchial stump insufficiency during the 15-month follow-up.² Although this series did not use radiation preoperatively, and all patients had mesothelioma, this recent series shows that excellent surgical results can be achieved even with all patients undergoing pneumonectomy, chemotherapy, and radiation by frequent use of muscle flaps.

Three-dimensional, conformal 4500 cGy XRT with concurrent chemotherapy using cisplatin 20 mg/m² and etoposide 50 mg/m² was applied to a group of patients with stage IIIA non-small cell lung cancer (NSCLC) in a study by Pourcel and colleagues.³ Three to 4 weeks after CRT, patients were reassessed for surgical candidacy. Surgery was

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completed 4 to 6 weeks after CRT. Inoperable patients received an additional 20 to 25 Gy boost or 1 extra cycle of cisplatin + etoposide. A total of 107 patients received induction CRT followed by surgery. There were 18 stage IIB-Pancoast tumors, 58 IIIA tumors, and IIIB tumors found in 31 patients. Squamous cell carcinoma was found in 48%, adenocarcinoma was found in 44%, and large-cell carcinoma was found in 14% of patients. Seventy-two patients (67%) underwent resection, including pneumonectomy in 21, lobectomy in 45, and bilobectomy in 5. Carcinoma was found to be unresectable in 1 patient. Macroscopic complete resection was achieved in all other patients. In the 3-month postoperative period, 5 patients (6.9%) died, including 4 patients after pneumonectomy (right in 3 patients, left in 1 patient). A pathologic complete response or microscopic residual foci were found in 39.5%. Two and 3-year overall survivals were 55% and 40%, respectively, and median survival times were 62% and 51%, respectively (median = 36.5 months) for 71 patients undergoing resection. Multivariate analysis demonstrated surgical resection and tumor necrosis greater than 50% (or pathologic complete response) were predictive factors of the risk of death (hazard ratio = 0.50 and 0.48, $P = .006$ and $.038$, respectively). The authors concluded that pneumonectomy carries a high risk of postoperative death (particularly right pneumonectomy) after induction CRT.³

In a series from the Brigham and Women's Hospital, pneumonectomy was performed in 73 patients after radiation (median dose 54 Gy); 69 patients (95%) received concurrent CRT. The median age was 62 years; 43 patients (59%) were male. Thirty-seven patients (51%) had stage IIIA NSCLC, 27 patients (37%) had stage IIIB NSCLC, 6 patients (8.2%) had stage IIB NSCLC, and 4 patients (5.4%) had stage IV NSCLC (with solitary brain metastasis). Forty-four patients (60%) received carboplatin and paclitaxel chemotherapy. Fifteen patients (21%) received cisplatin and etoposide as induction. Forty-five patients (62%) underwent left pneumonectomy, and 28 patients underwent right pneumonectomy. One- and 2-year overall survivals were 70% and 49%, respectively. The 30- and 100-day mortalities were 6% and 10%, respectively. Four of 73 patients (6%) died of acute respiratory distress syndrome. Nonfatal treatment-related morbidity was 11%. Univariate analysis demonstrated that right-sided pneumonectomy was associated with a higher risk of treatment-related mortality ($P = .099$), although these authors continue to use pneumonectomy in carefully screened patients.⁴

In a series of stage IIIA-N2 NSCLCs, 71 patients (60 male, median age of 60 years) received a 2-drug platinum-based regimen followed by XRT (20–40 Gy). There were 9 complete and 27 partial responses. Surgery included lobectomy (44%) and left (15.5%) and right (27%) pneumonectomies. Operative mortality was 4.2%, and 21 patients (29%) had postoperative complications. Median survival was 17

months. Three and 5-year survivals were 24% and 13%, respectively. Five-year survival was worse in patients with postoperative complications. Multivariate analysis identified male gender and postoperative persistent positive lymph nodes (LNs) as significant predictors ($P = .002$). The authors concluded that pathologic response after CRT for patients with stage IIIA-N2 NSCLC enables a better survival.⁵

In a series from Toronto, 40 patients with biopsy-proven T1-3 N2 M0 NSCLC underwent induction CRT before surgical intervention; 25% of patients had T1 tumors, 62.5% of patients had T2 tumors, 7.5% of patients had T3 tumors, and 5% of patients had T4 tumors. Induction chemotherapy included cisplatin 50 mg/m² and etoposide 50 mg/m². Patients underwent concurrent daily external beam XRT to 45 Gy. Lung resection was undertaken within 6 weeks of completion of CRT. Two further cycles of consolidation chemotherapy were then given if tolerated. Overall and disease-free median survivals were 40 and 37.1 months, respectively. Overall and disease-free 3-year survivals were 51.7% and 52.3%, respectively. R0 resection was achieved in 92.5% of patients. Operative mortality was 7.5% (0% for lobectomy; 27% for pneumonectomy). All mortalities occurred within the first 2 years of the experience. The authors concluded that CRT before pulmonary resection in carefully selected patients with surgically resectable stage IIIA (N2) NSCLC can lead to improved overall and disease-free survival. Although pneumonectomy carried a higher risk of postoperative complication, the authors found the learning curve reasonable.⁶

In a series from Chicago, 26 patients with NSCLC with N2 disease underwent preoperative concurrent platinum-based chemoradiotherapy with a dose of 58 Gy. The mortality rate was 7.7% (2 patients). Three patients (11.5%) had minor complications. Downstaging was demonstrated in 76.9% of patients. A pathologic complete response rate of 34.6% was found. Downstaging of mediastinal LNs was observed in 20 of 26 patients. One- and 3-year survivals were 80.2% and 45.7%, respectively. One- and 3-year disease-free survivals were 76.9% and 37.3%, respectively. For patients with mediastinal downstaging, disease-free survival was 79.2% versus 0% ($P = .0001$). Differences in XRT dose (50–60 Gy) and chemotherapy regimens did not significantly affect pathologic downstaging rates, complete response rates, disease-free survival, or survival.⁷

A total of 139 patients (100 male and 39 female) underwent induction therapy and surgery for stage IIIA and IIIB NSCLC in a study from Rome, Italy. The mean age was 58.4 ± 7.7 years. A total of 109 patients received chemotherapy (with cisplatin and gemcitabine); 30 patients received chemoradiotherapy (XRT median dose 50 Gy). Complications developed in 49 patients (35%). These included persistent air leakage (23%–30% of lobectomies), cardiac complications, respiratory failure, and infections. Five patients (3.5%) died in the postoperative period. Five patients

who underwent pneumonectomy died (mortality of 12.5%). Only pneumonectomy was associated with an increased mortality risk with no differences between intra- and extrapleural dissection or right and left pneumonectomies. The authors concluded that pneumonectomy is associated with an increased risk of mortality and should be performed only in carefully selected patients.⁸

A recent phase I/II trial (UMGCC 9953) was reported by the author's group in patients with stage IIIA/B NSCLC who underwent induction CRT followed by surgery and consolidation chemotherapy. In phase I, escalating doses of carboplatin and vinorelbine were used with concurrent 69.6 Gy hyperfractionated XRT. In the phase II portion of the study, identical XRT with chemotherapy at maximal toxic dose from the phase I was used. Surgical resection was undertaken if mediastinal nodal clearance was proven by repeat mediastinoscopy, thoracoscopy, or thoracotomy. Consolidation chemotherapy consisted of carboplatin/vinorelbine for 3 cycles followed by docetaxel for 3 cycles. Forty-seven patients were enrolled in the study. There were 5 T4 tumors, 18 N2 tumors, and 8 N3 tumors found in 31 patients. Pre-treatment staging was IIIA in 33 patients and IIIB in 14 patients. There were 15 men and 32 women with a mean age of 56 years. Twenty-eight patients completed trimodality with surgery, including 22 lobectomies, 4 pneumonectomies, and 1 wedge resection. The postoperative mortality and morbidity were 0% and 36%, respectively. Complications included 2 minor and 1 major (ventilator dependence). The pathologic complete response rate was 28.6%. The median survival time for the entire cohort (n = 47) was 29.6 months. The median survival time was 55.8 months for patients with mediastinal nodal clearance (n = 28).⁹

Intergroup 0139 was a prospective trial designed to determine the benefit of surgical resection after CRT. Although the overall survival was better for patients undergoing surgical resection and disease-free survival was improved, the study was skewed by poor postoperative results in patients undergoing pneumonectomy, with a 26% mortality in this subgroup. In a recent reanalysis of these data, when patients with pneumonectomy were excluded, the results were statistically improved for patients undergoing lobectomy alone after CRT.¹⁰

In a recent study by Gamliel and colleagues,¹¹ 28 patients (8 female) with a mean age of 53.4 years underwent pneumonectomy after neoadjuvant CRT. The preoperative regimen included concurrent chemotherapy with platinum/etoposide or carboplatin/paclitaxel with concurrent XRT to 61.2 Gy. The mean interval between XRT and resection was 67.1 days. All but 1 patient had downstaging, and 15 of 28 patients (53%) had a pathologic complete response. All patients were discharged alive from the hospital. The mean length of stay was 8.6 days. There was 1 death within 30 days. There were 14 major complications, including 1 patient with esophageal stricture, 3 patients with vocal cord

paralysis, 4 patients with postoperative respiratory distress, 2 patients with arrhythmias, 1 patient with upper-extremity venous thrombosis, and 3 patients with bronchopleural fistulae (1 fatal, 1 treated conservatively, and 1 muscle flap was done as a reoperation).¹¹

Currently, Radiation Therapy Oncology Group 0229 is a phase II trial of concurrent chemotherapy and high-dose XRT followed by surgery in stage III NSCLC.¹² This study allows patients to undergo curative resection after high-dose CRT. Preliminary data on these 60 patients will be important in the near future when they are reported.

The current study by Boffa and colleagues¹ describes 232 patients who underwent pneumonectomy at Massachusetts General Hospital over a period of 20 years. A total of 201 underwent a preoperative mediastinoscopy. Seventy-three patients underwent combined modality treatment (CRT). Fifty-nine patients had CRT preoperatively, 8 patients had preoperative chemotherapy alone, 8 patients had preoperative XRT, and 8 patients had remote XRT. The mean XRT dose was 50 Gy. There were 112 right and 120 left pneumonectomies. There were 21 carinal pneumonectomies (6 of whom had CRT preoperatively). The bronchial stump was covered with pericardial fat in 120 patients, and intercostal muscle flaps were used in 64 patients. The overall 30- and 90-day mortalities were 9% and 13.4%, respectively. The mortality was 7.4% for patients after induction therapy and 10% for those with no preoperative therapy. Patients with right pneumonectomies fared worse than patients with left pneumonectomies, although this was not true for those patients who underwent induction therapy. Morbidity included 12 bronchopleural fistulae (5%); 75% of these patients subsequently died. Pulmonary edema was more common in patients who underwent resection alone. Multivariate analysis demonstrated that preoperative cardiac illness, forced expiratory volume in 1 second less than 1 liter, steroid use, and increased blood loss were poor prognosticators. Early extubation and negative LN at resection were good prognosticators.

DISCUSSION

This counterpoint depicts the current state of the literature on pneumonectomy after CRT. Although several large series have been quoted, there are no level 1 data to support either performing or not performing pneumonectomy in this setting. With this in mind, all the experiences cited herein, as well as those cited in the article by Boffa and colleagues,¹ must be taken with a grain of salt. The main limitation of the article by Boffa and colleagues is the retrospective nature of the review. In addition, there are many subgroups that were included that might be best left out of this study. If we focus only on the subset of 59 patients who had CRT preoperatively, there still is an impressive result with only a 7.4% mortality and low leak rate. These authors have found that poor cardiac or pulmonary status, steroid use, and blood loss are prognosticators of a bad outcome.

TABLE 1. Summary of results of pneumonectomy after CRT

First Author	Reference	Chemotherapy	Radiotherapy dose	Morbidity	Mortality
Beshay	2	Cis/gem	54	25%	3%
Pourel	3	Cis/eto	45		(4/21) 19%
Allen	4	Carbo/tax Cis/eto	54	11%	6%
Barle'si	5	platinum	20–40	29%	4.2%
Uy	6	Cis/eto	45		27%
Shaikh	7	platinum	58		7.7%
Venuta	8	Cis/gem	50	35%	12.5%
Edelman	9	Carb/vinor	69.6	36%	0%
Albain	10	Cis/eto	45	25%	26%
Gamliel	11	Cis/eto Carbo/taxol	61.2	50%	3.5%
Boffa	1	Platinum	50	25%	9%

The role of pneumonectomy after CRT is an important topic of study as more patients are being offered aggressive therapy for stage IIIA and IIIB disease. Since the Intergroup trial demonstrated a mortality of 26% in a prospective, randomized study, use of pneumonectomy in this setting has faced significant criticism.¹⁰

The studies cited in this article report a mortality from 3% to 27% for pneumonectomy after CRT (Table 1). Several single institution studies, including recent studies reviewed in this article, suggest a mortality not nearly as high as that found in the Intergroup trial. The current article by Boffa and colleagues¹ reports a mortality ranging from 7% to 13.4% depending on whether induction therapy and right or left pneumonectomy was performed. Additional criticism is that most analyses do not include all patients seen at the institution as an intent-to-treat analysis; that is, the overall number of patients with IIIA or IIIB disease is generally not available to the reader. One must assume that there are other patients who underwent induction chemotherapy or even combination CRT who did not go on to surgery. These patients were generally excluded from surgery because of progression of disease, lack of mediastinal nodal sterilization, or deterioration in their medical condition. This denominator, if available, would help the analysis of many of these articles. The only true prospective data analysis remains the Intergroup study, which included a lower radiation dose and was performed at a number of centers, probably reflecting a “real life” mortality when this procedure is offered at institutions that are perhaps not considered “centers of excellence” for this kind of surgery.

One of the main limitations in the current study, as well as the many other single institution or phase 2 trials, is the lack of standardization in staging and restaging. If all patients undergo pretreatment positron emission tomography scanning and pathologic LN sampling, the denominator would then clearly be patients with proven pathologic N2/N3 disease. In addition, these patients would then be stratified to bulky versus nonbulky disease, microscopic versus macroscopic,

and even single-station versus multiple-station disease. Each of these subgroups might have different survivals if clearly evaluated prospectively. Finally, restaging using positron emission tomography/computed tomography followed by pathologic staging using needle biopsy, mediastinoscopy, repeat mediastinoscopy, or video-assisted thoracic surgery would further refine which patients then go on to resection and appropriately identify subsets of patients who are pathologic responders from those who are nonresponders. Again, it is likely that survival would be correlated to these findings. Lacking this type of specific staging data, we are left to rely on previous studies that did identify subgroups of survivors and assume that we can extrapolate those data to these studies.

Surgical considerations when offering pneumonectomy after CRT include coverage of all bronchial stumps with muscle flaps. Serratus anterior flaps are generally used by our group for pneumonectomies, and intercostal muscle flaps are used for lobectomies. Limited intraoperative fluid administration is allowed in an attempt to minimize acute respiratory distress syndrome. Barotrauma to the contralateral lung is limited during single-lung ventilation by limiting peak airway pressures and ventilatory volume. Also, every attempt is made to achieve early extubation after the completion of the resection.

CONCLUSIONS

On the basis of the review of these recent studies, it would seem that although there may be a benefit to lung resection after CRT, the morbidity and mortality of performing a pneumonectomy are prohibitive. Unless specific subsets of patients can be identified, such as those with pathologic LN response or with limited or no comorbidity, this extensive surgery should be used cautiously or perhaps only in the context of a clinical prospective trial.

Despite the data presented in this counterpoint, I believe that Boffa and colleagues¹ are correct in their conclusion. Selected patients, especially those who are LN negative after

preoperative CRT, who are otherwise fit, relatively young, with few if any cardiac risk factors for right- or left-sided heart failure, should be offered a pneumonectomy for definitive therapy. I agree that even a right pneumonectomy can be performed safely with acceptably low morbidity and mortality in selected patients at selected centers. This approach requires an audacious surgical team, with technical experience to gain easy proximal control of fragile intrapericardial arteries and veins, the potential for bypass backup, and an ability to rotate multiple, complex muscle flaps at the time of the first surgery. Although this may not be doable in all centers, those who have significant experience should be encouraged to continue to offer this lifesaving option for these patients with an otherwise fatal disease.

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