POINT: Operative risk of pneumonectomy—Influence of preoperative induction therapy

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Background: Prior data indicate increased perioperative morbidity and mortality in patients receiving induction chemoradiotherapy before pneumonectomy for lung cancer.

Objective: We reviewed a consecutive series of pneumonectomies to determine the impact of induction therapy on operative mortality.

Results: Over a 15-year period, 183 patients underwent pneumonectomy for lung cancer. Forty-six received combined preoperative radiochemotherapy (25.2%), and 137 patients underwent resection only. Indications for induction therapy were stage IIB disease in 1, IIIA in 35, IIIB in 8, and IV in 2 patients. Patients receiving induction therapy were younger (mean age 58.4 vs 61.9 years; $P = .033$), had less heart disease (6.5 vs 26.3%; $P = .0035$), higher preoperative forced expiratory volume in 1 second (2.48 vs 2.13 L; $P = .0018$), a lower rate of endobronchial tumor (34.8 vs 67.2%; $P = .0002$), and underwent intrapericardial procedures more often (71.7 vs 43.1%; $P = .0011$). Hospital mortality was 4.3 % (2/46) after preoperative therapy and 6.6% (9/137) after resection only ($P = .73$); the difference in cardiopulmonary morbidity was not significant (51.1% vs 40.4%; $P = .22$). Induction did not predict hospital mortality after adjustment for a propensity score derived from nonoperative and operative variables correlated with neoadjuvant therapy.

Conclusions: A regimen of induction radiation and chemotherapy does not increase the operative mortality of pneumonectomy in carefully selected patients.

As the most extensive anatomic lung resection, pneumonectomy has the highest operative mortality. The administration of preoperative adjuvant therapy before pneumonectomy is controversial because of the potential to increase this risk. Trimodality therapy was, for example, associated with high mortality in a phase II multi-institutional prospective randomized trial, particularly for right-sided procedures.[1] Conversely, patients with locally advanced lung cancer stand to receive the greatest benefit of additional up-front tumor therapy, and limiting patients with large tumors and N2 disease to surgical resection first risks progression to systemic disease.

We[2] have used combined radiotherapy and chemotherapy for the preoperative treatment of N2 disease and selected other indications since the late 1980s[2] and reviewed our experience during a period of consistent application of neoadjuvant radiochemotherapy to examine mortality and its predictive factors.

METHODS

Medical records of a consecutive series of patients with lung cancer undergoing pneumonectomy by the Division of Thoracic Surgery at Massachusetts General Hospital were reviewed. Complex procedures were excluded as outlined in Figure 1. The Partners Human Research Committee approved the study. Demographic data, preoperative pulmonary function, and scintigraphic ventilation–perfusion data were obtained. Comorbid conditions were recorded. *Hypertension* was defined as taking antihypertensive medication to lower blood pressure, *diabetes mellitus* as taking oral or parenteral medications to lower blood sugar, and *congestive heart failure* as past hospital admissions at any time or taking diuretics or angiotensin-converting enzyme inhibitors for this diagnosis or having symptoms related to reduced left ventricular ejection fraction. *Coronary artery disease* was defined as a past myocardial infarction or evidence of myocardial ischemia by electrocardiogram or stress testing or known stenosis after cardiac catheterization. *Renal failure* was defined as a creatinine level above 1.6 mg/dL and *peripheral vascular disease* as the presence of symptoms of claudication or past surgical or catheter-based intervention for this indication. The diagnoses of *cerebrovascular accident* or *transient ischemic attack* were assumed after permanent or temporary focal neurologic deficits. Patients underwent computed tomography (CT) of the chest, evaluation of the brain by either CT or magnetic resonance imaging, and either bone scan or, since its inception, positron emission tomography. With the exception of patients referred to Massachusetts General Hospital after combined induction, all patients were evaluated by a thoracic surgeon before treatment, almost always including mediastinoscopy. No mediastinoscopy was repeated after induction therapy; restaging occurred with CT.

Neoadjuvant preoperative treatment consisted of combined chemotherapy and radiation. There was no uniform protocol during the study period,

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Abbreviations and Acronyms
CT = computed tomography
FEV_1 = forced expiratory volume in 1 second

and numerous patients were treated at outside institutions; however, the standard preoperative radiation dose was administered in 25 fractions over a period of 5 weeks, in combination with chemotherapy, limiting the dose to the main bronchus to 45 Gy. We have used a higher radiation dose (54 Gy) in selected extensive tumors. Some patients were referred after neoadjuvant therapy having received doses in excess of 60 Gy. At Massachusetts General Hospital, there was a change from 2- to 3-dimensional conformal radiotherapy in 2001. Patients with prior cervical or mediastinal radiation for other indications were excluded.

The perioperative management was standardized regarding routine use of epidural catheters, intravenous fluid restriction, operative use of vasoactive drugs, and low tidal volumes during 1-lung anesthesia. A chest catheter was placed at the conclusion of the operation in all patients and removed either immediately after extubation or the next day. Intraoperative parameters studied were total duration, blood loss, transfusion requirement, epidural pain control, intraoperative hypotension, and operating room extubation.

Postoperative variables examined were reintubation, adult respiratory distress syndrome, pneumonia, pulmonary embolism, pulmonary edema, empyema, bronchopleural fistula, myocardial infarction, atrial fibrillation, ventricular fibrillation, congestive heart failure (grouped as major cardiopulmonary events), duration of mechanical ventilation, tracheostomy, reoperation, deep vein thrombosis, neurologic complication, and gastrointestinal complication. The hospital mortality was determined.

Tumors were staged according to published revisions of the international lung cancer staging system.[3] The resection was complete if specimen margins, including bronchial, vascular, and soft tissue margins, were found to be free of tumor.

Statistical Analysis

Univariate analysis was conducted by Fisher's exact test for binary variables and the Wilcoxon exact test for continuous variables. The variables selected for calculation of a propensity score[4] included all nonoperative and operative variables correlated with induction therapy or mortality in univariate analyses (except for highly correlated measurements, for example, forced expiratory volume in 1 second (FEV_1) and forced vital capacity, when only one was used).

The propensity score was calculated as follows:

$$p = exp(L)/(1 + exp[L])$$

Where L is a linear function:

$$L = -7.106461 + 0.008476\ age - 0.290960\ l1 + 0.19304\ l2 - 0.152798\ l3 - 2.096960\ l4 - 1.513946\ l5 + 1.015116\ pN\ classifier - 0.797669\ pT\ classifier + 0.687062\ FEV_1 + 0.035041\ DLCO\% + 0.400145\ l6 + 0.023664\ l7 + 1.580099\ l8 + 1.854619\ l9 + 1.995547\ l10 + 0.917844\ RBC\ packs$$

l1 = 1 if male sex, 0 otherwise
l2 = 1 if renal disease present, 0 otherwise
l3 = 1 if hypertension present, 0 otherwise
l4 = 1 if CAD or CHF present, 0 otherwise
l5 = 1 if bronchial tumor mass present, 0 otherwise
l6 = 1 if FEV_1 is missing, 0 otherwise
l7 = 1 if DLCO% is missing, 0 otherwise
l8 = 1 if intrapericardial procedure, 0 otherwise
l9 = 1 if beta-blockers were used during operation, 0 otherwise
l10 = 1 if extubation after operation was immediate, 0 otherwise.

CAD = coronary artery disease; CHF = congestive heart failure; DLCO = carbon monoxide diffusion capacity; FEV_1 = forced expired volume in 1 second; absorbed radiation dose; RBC = red blood cell; T, N = TNM classifier; pT, pN = pathologic T resp. N.

The coefficients in the above linear function are maximum likelihood estimates obtained by logistic regression.

To determine whether induction therapy predicted hospital mortality, we used the propensity score as a variable in a logistic regression along with induction therapy.

RESULTS

From September 1993 to December 2007, 183 consecutive patients underwent pneumonectomy for non–small cell carcinoma of the lung at Massachusetts General Hospital. Their mean age was 61.1 years and 114 (62.3%) were male. Comorbidity was present in 109 (59%) patients: hypertension in 43%, coronary artery disease or congestive heart failure in 21%, diabetes mellitus in 7.7%, and steroid use in 6.0%. Eleven patients had received oral steroid therapy, 9 for reactive airway disease, 1 for radiation pneumonitis, and 1 after liver transplantation. Table 1 lists demographics and preoperative

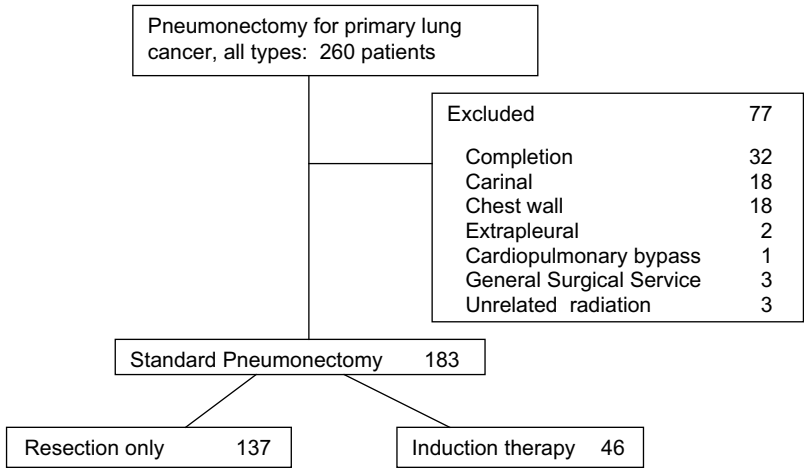

FIGURE 1. Composition of study group and excluded patients.

parameters for patients with and without preoperative therapy. Patients receiving preoperative treatment were younger, had fewer cardiac comorbidities, and had better lung function. Mediastinoscopy preceded resection in 96% of patients.

Preoperative Therapy

Forty-six (25.1%) of 183 patients received combined mediastinal radiation and chemotherapy. The clinical stage of patients treated with induction therapy was IIB in 1, IIIA in 35, IIIB in 8 (T4 in 2, N3 in 6), and IV in 2 patients. The chemotherapy regimen was cisplatinum/vinorelbine/5-fluorouracil in 20 patients, carboplatin/taxol in 17, cisplatinum/VP16 in 4, cisplatinum/taxol in 1, cisplatinum/VP16/taxotere in 1, and was not recorded in 3. Complications of chemotherapy occurred in 11 patients, including neutropenia in 5, pneumonia in 3, and severe nausea in 3. The median radiation dose was 45 Gy (range 42–72 Gy), but preoperative therapy rarely exceeded 54 Gy. Radiation was complicated by pneumonitis in 3, esophagitis in 7, and important dysphagia in 2 patients.

Resection

In the induction group, 24 patients underwent left and 22 right pneumonectomy, whereas no neoadjuvant therapy was given to 52 having right-sided and 85 having left-sided resections. Table 2 lists operative parameters. Patients receiving induction had a higher proportion of intrapericardial procedures, required a greater number of transfusions, were more likely to receive beta-blockers, and less often had a bronchial mass on endoscopy.

Operative Events

The estimated median blood loss as determined from anesthesia records was 300 mL; estimated blood loss exceeded 1000 mL in 10 patients. Twenty-five (13.7%) patients received intraoperative red blood cell transfusions. Bronchial stump coverage with vascularized tissue was described in all but 3 patients and consisted in the induction group of intercostal muscle in 23, pericardial fat in 10, omentum in 6, latissimus muscle in 4, and pleura in 3. All but 8 patients were extubated in the operating room; blood loss in 3 of these was 1000 mL or greater. Median operating time was 290 minutes.

Pathologic Results

The histologic type of carcinoma was squamous in 95, adenocarcinoma in 73, large cell in 8, adenosquamous in 6, and bronchioalveolar in 1. The pathologic stage is listed in Table 3. Eight patients had M1 disease as a result of either solitary brain metastasis (3 patients) or ipsilateral carcinoma of identical histologic type in a separate lobe (5 patients: adenocarcinoma 4 and adenosquamous 1). Microscopically positive margins were identified in 9 (4.9%) resections. Hilar soft tissue was positive in 5, the perivascular margin in 2, and the atrial margin in 1 patient. There were no grossly incomplete (R2) resections. In the induction group, 9 (19.5 %) of 46 patients had a complete pathologic response.

Mortality and Morbidity

The overall hospital mortality was 6.0% (11/183). There was no hospital death during the last 5 years of the study period. Table 4 lists the procedure-specific mortality. Hospital mortality for right pneumonectomy was higher than for left pneumonectomy, but induction therapy was not associated with increased mortality. No patient with stage IV disease and 1 patient with stage IIIB (T4 N0) died.

Causes of hospital death are given in Table 5. Adult respiratory distress syndrome or postpneumonectomy pulmonary edema in 4 patients was the leading cause of death. Hospital morbidity is listed in Table 6. A bronchopleural fistula was confirmed in 5 patients (2.7 %, 2 right and 3 left), of whom 1 received induction therapy and 2 died during hospitalization. The only difference in the rates of individual or combined cardiopulmonary morbidities was a higher tracheostomy rate in the induction group (8.9% vs 1.5%; $P = .034$).

Multivariate Analysis

The nonoperative and operative variables that entered in the multivariable model and predicted induction therapy were the absence of a bronchial tumor mass ($P = .0019$),

TABLE 1. Demographic data and nonoperative risk factors

Variable	No induction	Induction therapy	*P* value
No.	137	46	
Age, y (mean ± SD	61.9 ± 11.5	58.4 ± 10.0	.0334
Male gender (%)	62.8	60.9	.8613
Hypertension (%)	43.8	39.1	.6094
Diabetes (%)	7.3	8.7	.7530
Steroid use (%)	5.8	6.5	1.0000
CHF (%)	8.8	0.0	.0391
CAD (%)	21.2	6.5	.0247
CAD or CHF (%)	26.3	6.5	.0035
Renal failure (%)	2.9	4.3	.6421
Peripheral vascular disease (%)	8.0	8.7	1.0000
Cerebrovascular accident (%)	6.6	4.3	.7331
Transient ischemic attack (%)	2.2	2.2	1.0000
Preoperative hematocrit ± SD	37.9 ± 4.6	35.2 ± 4.1	<.0001
Preoperative radiotherapy (%)	0	91.4	<.0001
FEV_1 ± SD	2.13 ± 0.71	2.48 ± 0.64	.0018
FEV_1 ± SD (%)	70.6 ± 19.6	80.5 ± 19.0	.0026
FVC ± SD	3.02 ± 0.96	3.41 ± 0.84	.0187
DLCO ± SD (%)	69.6 ± 19.0	78.5 ± 19.4	.0721
Scintigraphy			
Perfusion in remaining lung (%)	67.5 ± 14.0	63.5 ± 9.4	.1574
Ventilation in remaining lung (%)	62.7 ± 15.0	58.0 ± 9.0	.1193

SD, Standard deviation; *CHF*, congestive heart failure; *CAD*, coronary artery disease; *FEV_1*, forced expiratory volume in 1 second; *DLCO*, carbon monoxide diffusion capacity.

TABLE 2. Operative variables in patients with and without induction therapy

Variable	No induction (n = 137) %	n	Induction therapy (n = 46) %	n	*P* value
Mediastinoscopy	96.4	132	93.5	43	.4167
Bronchial tumor mass	67.2	92	34.8	16	.0002
Epidural pain control	99.3	136	100.0	46	1.0000
Right pneumonectomy	38.0	64	47.8	48	.2976
Intrapericardial procedure	43.1	59	71.1	33	.0011
Total duration (min ± SD)	288 ± 90		314 ± 108		.2685
Operative hypotension	19.4		19.6		1.0000
Operative beta-blocker use	7.8		21.7		.0154
Operative vasopressor use	62.8		63.0		1.0000
Extubation in OR	95.6		95.7		1.0000
Total blood loss (mL ± SD)	371 ± 261		445 ± 371		.2087
RBC units (±SD)	0.19 ± 0.63		0.70 ± 1.72		.0057
Mean duration of intubation (days ± SD)	1.16 ± 0.44		1.13 ± 0.34		.7836
pT classifier	2.40 ± 0.64		2.11 ± 0.61		.0124
pN classifier	0.82 ± 0.64		1.25 ± 0.89		.0017

SD, Standard deviation; *OR*, operating room; *RBC*, red blood cell; *pT pN*, pathologic T resp. N.

a higher pN classifier ($P = .0019$), intrapericardial procedure ($P = .0022$), the absence of coronary artery disease or congestive heart failure ($P = .015$), intraoperative beta-blocker use ($P = .015$), more units of blood transfused ($P = .016$), and higher carbon monoxide diffusion capacity (odds ratio 1.04; $P = .017$). Age, sex, renal disease, hypertension, FEV_1, and immediate extubation did not predict induction therapy. The propensity score was entered, as a variable, in a logistic regression for hospital mortality. Induction therapy did not predict hospital mortality, after adjustment for propensity score (Table 7).

Induction therapy remained nonpredictive for hospital mortality when this model was adjusted for additional variables. Hypertension, present in 45% of survivors and only 9.1% of operative deaths ($P = .026$), modestly lowered the odds of mortality (Table 8).

When only nonoperative or preoperative variables were entered in this model to determine the propensity score, induction therapy again failed to predict operative death.

TABLE 3. Pathologic stage after pneumonectomy

	No induction	Induction therapy
Stage I		
T2 N0	21	9
Stage II		
T1 N1	1	1
T2 N1	52	7
T3 N0	14	0
Stage IIIA		
T3 N1	16	0
T1-3 N2	17	16
Stage IIIB		
T4 N0-2	10	1
T2 N3	0	1
Stage IV		
Any M1	6	2
Complete response		9

DISCUSSION

There is disagreement concerning whether neoadjuvant therapy raises the operative risk of pneumonectomy. In contrast to several retrospective studies that found increased respiratory complications[5] but no increase in mortality after induction chemotherapy,[6,7] a recent prospective randomized study, Southwest Oncology Group phase II 8805, examining induction trimodality therapy, reported a higher operative mortality, in particular after right pneumonectomy.[1] Other retrospective studies[8-10] also reported risks for pneumonectomy that exceeded a recently reported 6% mortality of standard pneumonectomy in the Society of Thoracic Surgeons Thoracic Database.[11] The preliminary analysis of intergroup trial 0139 found an early mortality of 24% after right pneumonectomy.[12] These reports overlap with existing knowledge of increased operative mortality and morbidity after resection of the right lung in comparison with left-sided procedures.[13] The awareness of this risk is expected to influence the choice and sequence of multimodality therapy for locally advanced lung cancer and may narrow already limited treatment options. However, the attribution of higher mortality rates to preoperative therapy is not conclusive; institution-specific selection criteria for pneumonectomy, extent of evaluation of comorbidity, and use of surgical strategies to

TABLE 4. Procedure-specific mortality

Type of pneumonectomy	No. of procedures	Hospital mortality %	Hospital mortality No. of deaths
Total group	183	6.0	11
Induction therapy	46	4.3	2
Resection only	137	6.6	9
Right, induction therapy	22	4.5	1
Right, resection only	52	11.5	6
Left, induction therapy	24	4.2	1
Left, resection only	85	3.5	3

TABLE 5. Causes of hospital death

Cause	No induction	Induction therapy
Adult respiratory distress syndrome	3	1
Bronchopleural fistula	2	—
Myocardial infarction	2	—
Right heart failure	—	1
Pneumonia	1	—
Pulmonary hypertension	1	—
Hemorrhage	—	1
Ventricular fibrillation	1	—

In 2 patients, two causes contributing to death were listed.

TABLE 6. Hospital mortality and morbidity in patients with and without induction therapy

Variable	No induction (n = 137)		Induction therapy (n = 46)		*P* value
	n	%	n	%	
Death	9	6.6	2	4.3	.7331
ARDS	10	7.4	6	13.3	.2329
Pneumonia	15	11.0	7	15.6	.4351
Reintubation	12	8.8	5	11.4	.5672
Pulmonary edema	9	6.6	0	0.0	.1148
Bronchopleural fistula	4	2.9	1	2.2	1.0000
Empyema	5	3.7	1	2.2	1.0000
Reoperation	11	6.6	7	15.6	.1265
Pulmonary embolism	1	0.7	1	2.2	.4365
Tracheotomy	2	1.5	4	8.9	.0343
Myocardial infarction	3	2.2	0	0.0	.5750
Ventricular fibrillation	4	2.9	2	4.3	.6394
Congestive heart failure	4	2.9	1	2.2	1.0000
Atrial fibrillation	34	25.0	17	37.8	.1258
GI complications	7	5.1	4	8.9	.47
Neurologic events	8	5.9	4	8.9	.4963
Combined cardiopulmonary complications	55	40.4	23	51.1	.2278

protect the bronchial stump represent important factors that are difficult to capture and compare. Finally, the avoidance of pneumonectomy and trimodality therapy may lead to higher locoregional recurrence and lower survival.

In this retrospective analysis of pneumonectomy for lung cancer, neither operative mortality nor morbidity was increased in patients who received induction therapy before pneumonectomy for lung cancer. The effects of patient selection, demonstrated by the lower age and rates of comorbidity in the induction group, are obvious and appropriate to reduce operative risk. Propensity score analysis suggests, however, that the comorbid condition itself, and not neoadjuvant therapy, imparts risk under the existing conditions of patient selection. The result of this study supports the continued use of trimodality therapy before pneumonectomy and emphasizes the importance of rigorous and careful preoperative cardiopulmonary evaluation of operative candidates and meticulous operative technique.

On the basis of our results in patients with stage IIIA N2 disease in 1991,[2] we have preferred and continue to recommend to combine preoperative radiation and chemotherapy for clinical stage IIIA and selected stage II disease. Absence of disease in mediastinal lymph nodes after complete resection has proved in this and the Southwest Oncology Group 8805 study (in 10/42 patients, 24%,[2] vs 19/89 patients, 21%[1]) to be the strongest predictor of long-term survival. In addition to N2 disease, this approach included selected patients with large hilar tumors owing to concern for positive margins at the mediastinum. The complete response rate in the present study, 19.5%, is comparable with those in the

TABLE 7. Logestic regression for hospital mortality

Variable	OR	95% CI	*P* value
(Intercept)	0.059	0.025–0.136	<.0001
One unit of propensity score	3.074	0.180–52.387	.4377
Induction therapy	0.387	0.048–3.123	.3728

OR, Odds ratio; *CI*, confidence interval.

aforementioned studies. We have carefully selected these candidates for neoadjuvant radiochemotherapy and find our process validated. Given a selective approach to trimodality therapy, patients are not exposed to any greater operative risk by induction, a result similar to studies examining chemotherapy only.[5-7] The value of multimodality therapy in the case of pneumonectomy continues to be debated as the proportion of patients in prospective randomized studies is often small so that results rarely reflect consistent selection and surgical strategy.

Right pneumonectomy with or without preoperative cytoreductive therapy remains a formidable operation with important early postoperative risks. In our study, standard pneumonectomy had a 3-fold higher hospital mortality on the right than on the left despite younger patient age, confirming the results of others.[10,13] Potential causes for such imbalanced laterality risk include the greater threat of lymphatic outflow obstruction during right-sided lymph node dissections and the larger mass of the right lung. Parenchyma-sparing resections, furthermore, appear to thin out the ranks of candidates for right-sided resections more than on the left; in our earlier report of sleeve lobectomy, more than three fourths (78%) were right-sided procedures.[14] Others also have reported a higher number of right-sided sleeve resections[15] and left pneumonectomies.[13,15] Thus, the remaining right-sided tumors may consist of a selected group of larger, more invasive lesions in patients who may not tolerate preoperative therapy owing to comorbidity.

Our study has important limitations. First, the induction group in our study is small and may cause us to underestimate effects of induction on mortality. Further, neither we nor other investigators noted earlier include an analysis of candidates specifically rejected for this surgical procedure. Thus, the size and the survival of the rejected group are unknown, although we may infer that their survival is short. Our study also did not examine the precise tally of intraoperative and postoperative fluid management thought to be

TABLE 8. Odds of mortality

Variable	OR	95% CI	*P* value
Renal disease	58.637	3.291 – 1044.9	0.0056
Hypertension	0.049	0.003 - 0.870	0.0399
Immediate extubation	0.045	0.005 - 0.426	0.0068
RBC packs	1.417	0.741 - 2.708	0.2918
One unit of propensity score	8.463	0.126 - 566.8	0.3194
Induction therapy	0.072	0.002 - 2.548	0.1483

important in the origin of adult respiratory distress syndrome and postpneumonectomy pulmonary edema; in retrospective analysis, however, the precision for these variables is weak at best. The study period further encompassed important changes in patient management, the emphasis on intraoperative pressure control ventilation and the introduction of radiation techniques limiting exposure of the contralateral lung among them, reflected in a lack of operative deaths in the last 5 years. The changes were not the subject of our analysis but require separate study.

The selection of patients for induction therapy before pneumonectomy reflected in our results is also obvious in reports of preoperative high-dose (60 Gy) mediastinal radiation and chemotherapy that were achieved with perioperative mortality rates comparable with lower, standard radiation doses.[9,16,17] Median age in two of these studies was below 50 years, and mean FEV_1 was above 2.4 L in one. Stringent preoperative evaluation, careful operative technique including protection of the bronchial stump,[17] and a postoperative management dedicated to the particular risks of induction, even using elective postoperative mechanical ventilation,[16] may also explain these favorable results. Other factors including surgeon experience and hospital volume[18,19] have been associated with the operative outcome of pneumonectomy. Patient age, in contrast, may pose a less flexible limit to the benefits of careful selection, inasmuch as Mizushima and associates[20] found an 8-fold increase in operative mortality of pneumonectomy in patients over the age of 70 years. In our experience, patients receiving induction therapy were younger, but there was no difference in age between hospital survivors and patients who died. Patients with cardiopulmonary complications, however, were 5 years older than those without. Retrospective studies cannot be expected to disentangle the complexities of institutional selection and management, but may inform about the relative impact of risk factors.

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