Original Article

Primary pneumonectomy, pneumonectomy after induction therapy, and salvage pneumonectomy: a comparison of surgical and prognostic outcomes

Noriaki Sakakura, Tetsuya Mizuno, Hiroaki Kuroda, Yukinori Sakao

Department of Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya, Japan

Contributions: (I) Conception and design: N Sakakura; (II) Administrative support: N Sakakura; (III) Provision of study materials or patients: N Sakakura; (IV) Collection and assembly of data: N Sakakura; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Noriaki Sakakura, MD, PhD. Department of Thoracic Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. Email: nsakakura@aichi-cc.jp.

Background: Surgical outcomes of pneumonectomy for lung cancer differ based on various therapeutic strategies.

Methods: One hundred and fifty-one patients who underwent pneumonectomy were divided into three groups based on patients' therapeutic conditions: a primary pneumonectomy group (no preoperative treatment, n=137), an induction group (planned surgery after induction chemotherapy or chemoradiotherapy, n=10), and a salvage group (surgery for residual or enlarged lesions after radical non-operative therapies, n=4).

Results: Multivariate analysis showed that completeness of resection (P=0.003), subcategorization of whether there was no invasion, infiltration only to the main bronchus or pleura, or invasion of other deeper structures (P=0.008), and the presence or absence of mediastinal lymph node metastasis (P=0.033) were significant prognostic factors. Severe postoperative complications occurred in 5.1% (7/137), 20% (2/10), and 0% (0/4) in the primary pneumonectomy, induction, and salvage groups, respectively. Among patients with pN0-1 disease, the 3-year overall survival rate was 58.7% in the primary pneumonectomy group, 100% and 40% in cases with high and low pathological effects in the induction group, respectively, and 50% in the salvage group. Among patients with pN2 disease, this rate was 41.4% in the primary pneumonectomy group, and no patients survived for postoperative 2 years in the other groups.

Conclusions: For patients undergoing pneumonectomy, subcategorization based on the invasion status (none/bronchus/pleura or other deeper structures) is a crucial prognostic factor. To consider pneumonectomy in the induction or salvage setting, selecting patients with pN0-1 disease may be mandatory.

Keywords: Pneumonectomy; surgical and prognostic outcomes; long term survival; induction treatment; salvage surgery

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Introduction

According to the annual report of the Japanese Association for Thoracic Surgery, 38,444 cases of surgery performed to treat pulmonary malignancies in 2014 in Japan included 27,584 (71.8%) cases of lobectomy and only 521 (1.4%) cases of pneumonectomy, indicating that pneumonectomy is a rare treatment modality used for lung cancer (1). Understandably, after induction chemoradiotherapy to treat locally advanced lung cancer, pneumonectomy is even more uncommon. Data from the World Conference on Lung Cancer show that 88%

of 11,242 patients with IIIA-N2 non-small-cell lung cancer were treated with radical chemoradiotherapy, whereas 5% of these patients were treated with lobectomy after induction therapy, and pneumonectomy has been rarely used only in 1% of patients (2).

Although pneumonectomy after induction chemoradiotherapy may possibly be an inferior therapeutic strategy relative to radical non-operative chemoradiotherapy (3), contradicting positive results have also been obtained (4). Furthermore, pneumonectomy is performed very rarely as salvage resection after radical non-operative therapy for lung cancer (5-7). Positive outcomes reported after pneumonectomy (4) prompted us to reexamine all cases of pneumonectomy performed at our institution and to compare primary pneumonectomy with pneumonectomy after induction therapy and salvage pneumonectomy after radical chemoradiotherapy.

Methods

Study design and patients

This study was approved by the Institutional Review Board of the Aichi Cancer Center Hospital (approval No. 2017-1-330). Informed consent was obtained from each patient for the use of clinical data for various studies.

Among 3,989 patients who underwent pulmonary resection for lung cancer between 1990 and 2016 at our hospital, including those who underwent surgery after induction therapy (165 patients) and those who underwent salvage lung resection (18 patients), 151 consecutive patients who underwent pneumonectomy were examined. For retrospective analysis, these patients were divided into three groups: a primary pneumonectomy group (pneumonectomy without preoperative nonsurgical treatment, n=137), an induction group (pneumonectomy as planned pulmonary resection after certain preoperative treatment, n=10), and a salvage group (pneumonectomy defined as salvage surgery for a residual tumor after radical non-operative therapy or for enlarged lesions, n=4, *Table 1*). The induction group was defined as the group treated with ≥3 cycles of platinum-based chemotherapy or radical chemoradiotherapy. In the salvage group, tumor progression was comprehensively confirmed based on its enlargement observed on computed tomography, increased abnormal accumulation in lesions observed on positron emission tomography (PET), increased tumor marker levels, and other findings leading to pneumonectomy as salvage surgery wherein patients did not undergo any therapy other than surgery. Completion pneumonectomy was performed only in the primary pneumonectomy group (right, 2 patients; left, 6 patients) and was included in the study.

All patients were analyzed based on the eighth edition of the tumor-node-metastasis (TNM) staging classification system (8,9). In this study, the gross tumor size on pathological examination was used because reevaluation of the pathological invasive size of all tumors during the study period was difficult, and because the eighth edition for evaluating the lesion size was proposed in April 2016 after the proposal for a new classification in February 2016; cT and pT in the proposal of the eighth edition (8,9) and its validation (10) were still evaluated using the gross tumor size as done previously. The eighth edition affects the assessment of small lesions with a lepidic component to a greater extent; however, stage IB, II, and III tumors that were mainly examined in this study were considered solid lesions minimally affected by the method used for lesion size measurement compared with stage IA tumors. These points have been discussed previously (11). Completeness of resection was categorized to a complete (R0) or incomplete (R1/R2) resection based on the residual tumor status.

Pathological assessment

Pathological slides of resected lung specimens were prepared using a standard procedure. Briefly, the resected lung was inflated immediately and fixed by injection with 10% formalin. Sliced tissues were embedded in paraffin, and the blocks were sectioned and stained with hematoxylin and eosin. Elastin and immunohistochemical staining were performed when necessary. The histological effect (Ef.) of preoperative therapy was assessed using resection specimens on the following 5-point scale according to the General Rule for Clinical and Pathological Record of Lung Cancer (12): Ef.0, no effect, no morphological changes including degeneration or necrosis caused by treatment; Ef.1a, minor effect, viable cancer cells observed in two-thirds or more of cancer tissue; Ef.1b, mild effect, viable cancer cells observed in one-third or more and less than two-thirds of cancer tissue; Ef.2, moderate effect, viable cancer cells observed in less than one-third of cancer tissue; and Ef.3, marked effect, no viable cancer cells or residual cancer cells judged not to be viable.

Statistical analysis

The overall survival (OS) rate was calculated using the

Table 1 Baseline characteristics of 151 patients who underwent pneumonectomy[a]

Variable	Primary surgery group	Induction group	Salvage group
Number of patients	137 [90]	10 [7]	4 [3]
Age (years; range, median)	35–77 [62]	37–73 [61]	38–69 [59]
Sex			
Male	104 [76]	9 [90]	3 [75]
Female	33 [24]	1 [10]	1 [25]
Median follow-up (years; range)	3.1 [0.01–17.9]	1.7 [0.06–20]	1.8 [0.41–5.7]
Preoperative treatment			
Chemotherapy	–	9 [90]	0
Radiotherapy	–	0	0
Chemoradiotherapy	–	1 [10]	4 [100]
c-Stage			
I	24 [18]	0	0
II	48 [35]	4 [40]	1 [25]
III	64 [47]	6 [60]	3 [75]
IV	1 [0]	0	0
yc-Stage			
I	–	0	0
II	–	5 [50]	1 [25]
III	–	5 [50]	3 [75]
IV	–	0	0
Duration from the initial treatment to surgery (months; range, median)	–	3–5 [4]	8–30 [14]
Surgical site			
Right	40 [29]	7 [70]	1 [25]
Left	97 [71]	3 [30]	3 [75]
Morbidity/mortality[b]	7/2 [5/1]	2/0 [20/0]	0/0
Interstitial pneumonia	1/0	0/0	0/0
Bacterial pneumonia	1/0	0/0	0/0
Bleeding	1/1	0/0	0/0
Fatal arrhythmia	1/1	0/0	0/0
Bronchopleural fistula	1/0	2/0	0/0
Empyema	1/0	0/0	0/0
Postpneumonectomy syndrome	1/0	0/0	0/0
Resection			
Complete (R0)	106 [77]	9 [90]	4 [100]
Incomplete (R1/R2)	31 [23]	1 [10]	0

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Primary surgery group	Induction group	Salvage group
Histology			
Adenocarcinoma	45 [33]	1 [10]	1 [25]
Squamous cell carcinoma	70 [51]	6 [60]	2 [50]
Large cell carcinoma	14 [10]	2 [20]	0
Other	8 [6]	1 [10]	1 [25]
pT status			
T1a-b-c	8 [6]	1 [10]	1 [25]
T2a-b	54 [39]	3 [30]	1 [25]
T3	44 [32]	6 [60]	0
T4	31 [23]	0	2 [50]
Neighboring structures involved			
None	90 [66]	7 [70]	3 [75]
Main bronchus	8 [6]	0	0
T3 pleura[c]	12 [9]	0	0
T3 other organs	15 [11]	3 [30]	0
T4 organs	12 [8]	0	1 [25]
pN status			
N0	27 [20]	2 [20]	2 [50]
N1	53 [39]	5 [50]	0
N2	55 [40]	3 [30]	2 [50]
N3	2 [1]	0	0
pM status			
M0	122 [89]	10 [100]	4 [100]
M1a	11 [8]	0	0
M1b	4 [3]	0	0
p-Stage			
I	8 [6]	0	1 [25]
II	33 [24]	5 [50]	0
III	81 [59]	5 [50]	3 [75]
IV	15 [11]	0	0
Postoperative treatment			
Chemotherapy	18 [13]	1 [10]	0
Radiotherapy	3 [2]	1 [10]	0
Chemoradiotherapy	0	0	0

[a], data are presented as indicated or as the number of patients; [b], within 30 postoperative days; [c], parietal or mediastinal pleura. R, residual tumor status.

Kaplan-Meier method. OS was defined as the time from the date of surgery to that of all-cause death, and patients who were alive were censored on the last known date. Difference in survival rate was compared using the log-rank test and Cox proportional hazards model. All P values were two-sided, and P<0.05 was considered statistically significant. All statistical analyses were performed using JMP for Windows (version 9.0, SAS Institute, Cary, NC, USA).

Results

Patients' demographics

The patients' demographics and disease characteristics are summarized in *Table 1*. In the induction group, various chemotherapy regimens were used in three [cisplatin + vindesine + mitomycin], two (cisplatin + vinorelbine), one (cisplatin + docetaxel), three (carboplatin + docetaxel), and one (carboplatin + paclitaxel) patient, and one patient underwent chemoradiotherapy at a tumor bed boost dose of 60 Gy. In this group, postoperative pathological assessment of the resected specimens revealed that the Ef. obtained was mixed; Ef.0 was observed in three patients, Ef.1 in five patients (including one patient who underwent chemoradiotherapy), and Ef.2 in two patients; no Ef.3 was observed. Alternatively, all patients in the salvage group had a history of cisplatin-based chemotherapy and radical radiotherapy, followed by treatment with multiple chemotherapy regimens.

Mortality and morbidity

Severe perioperative complications, including interstitial pneumonia, bacterial pneumonia, fatal hemorrhage, fatal arrhythmia, bronchopleural fistula, and postpneumonectomy syndrome, were observed in 5.1% (7/137), 20% (2/10), and 0% (0/4) of patients in the primary pneumonectomy, induction, and salvage groups, respectively; these complications occurred frequently in the induction group but not in the salvage group. Among these, complication-related death within 30 postoperative days occurred in 1.5% (2/137) of patients in the primary pneumonectomy group but not in the induction and salvage groups. Death after 30 postoperative days but within 90 days occurred in 3.6% (3/137, cancer-related death), 10% (1/10, cancer-related death), and 0% (0/4) of patients in the primary pneumonectomy, induction, and salvage groups, respectively. In the induction group, severe morbidity occurred because of bronchopleural fistulas in two patients, one of whom was treated with chemoradiotherapy, although their bronchial stump was buttressed using an intercostal muscle flap. Although both patients were rescued by omentopexy, recurrence led to cancer-related death after 1.6 years in one patient and 1.8 years in the other patient.

Prognostic outcomes

The primary prognostic factors for all patients who underwent pneumonectomy are summarized in *Table 2*. Univariate analysis revealed that age, completeness of resection, tumor size, depth and sites of invasion of neighboring organs, and the pN factor were significant prognostic factors. The 3-year OS rate for patients without invasion of neighboring organs (n=100) was 54.8%, and those with infiltration only to the main bronchus or pleura (n=20) was 64.3%. Patients with pN2 disease showed significantly worse prognosis than those with pN0–1 diseases, but the significance decreased in multivariate analysis. Multivariate analysis revealed that completeness of resection (P=0.003) and subcategorization of involved neighboring organs (P=0.008) were more significant than the presence or absence of mediastinal lymph node metastasis (P=0.033) and were the crucial predictors in patients who underwent pneumonectomy. On the contrary, regarding the surgical site (right or left) of pneumonectomy, the prognosis tended to be slightly better for left side in this study, but failed to reach a statistically significant difference. Adjuvant therapy also seemed to be associated with better prognosis, but was not statistically significant.

There was no significant prognostic difference between different therapeutic strategies, with the 3-year OS rate being 51.7%, 39.4%, and 33.3% in the primary pneumonectomy, induction, and salvage groups, respectively (*Figure 1A*, *Table 2*). When the patients in the induction group were stratified based on the Ef., the 3-year OS rate was 100% in the Ef.2–3 group and 29.2% in the Ef.0–1 group (P=0.24), indicating a longer survival of patients in the Ef.2–3 groups (*Figure 1B*, *Table 2*).

The main study results were obtained by stratifying the above findings based on pN factor-based subcategorization (*Figure 2*). Among patients with pN0–1 disease (*Figure 2A*), the 3-year OS rate was 58.7% (n=80) in the primary pneumonectomy group, 100% (n=2) for patients with Ef.2–3 in the induction group, 40% (n=5) for patients with Ef.0–1 in the induction group, and 50% (n=2) in the salvage group. Among patients with pN2 disease (*Figure 2B*), this rate was 41.4% (n=57) in the primary pneumonectomy group,

Table 2 Summary of prognostic factors for patients who underwent pneumonectomy

Variable	N	Univariate analysis		Multivariate analysis		
		3-year survival rate (%)	P value	HR	95% CI	P value
Age (years)	104	57		1		
≤65						
>65	47	37.3	0.008	1.55	0.98–2.39	0.057
Surgical site						
Left	103	52.3				
Right	48	47.6	0.228			
Resection						
Complete (R0)	119	56.2		1		
Incomplete (R1/R2)	32	31.3	0.001	2.13	1.31–3.36	0.003
Tumor size (cm)						
≤5	91	60.1		1		
>5	60	36.7	0.021	1.59	1.02–2.45	0.039
Node status						
pN0–1	89	58.6		1		
pN2–3	62	39.5	0.002	1.59	1.04–2.45	0.033
Invasion						
None/bronchus/pleura	120	56.3[a]		1		
Other T3/T4 structures	31	28.5	0.001	1.97	0.32–0.83	0.008
Therapeutic conditions						
Primary surgery	137	51.7				
Surgery after induction therapy	10	39.4				
Ef.0–1	8	29.2				
Ef.2–3	2	100				
Salvage setting	4	33.3	0.6			
Postoperative therapy						
No	128	49				
Yes	23[b]	60.6	0.625			

[a], three-year overall survival rate for the invasion none group (n=100) was 54.8%, and that for bronchus or pleura group (n=20) was 64.3%; [b], right, 2; left, 21. CI, confidence interval; Ef., histological effect of preoperative therapy; HR, hazard ratio; R, residual tumor status.

and there were no patients with Ef.2–3 in the induction group. Three patients with Ef.0–1 in the induction group died of the underlying disease after 1.7 postoperative years. In the salvage group, one patient died of the underlying disease after 0.5 postoperative years, and another patient who survived had lung cancer recurrence. Among patients with pN2 disease, no patients in the induction and salvage groups survived to 2 years postoperatively.

Discussion

The possible prognostic factors after pneumonectomy

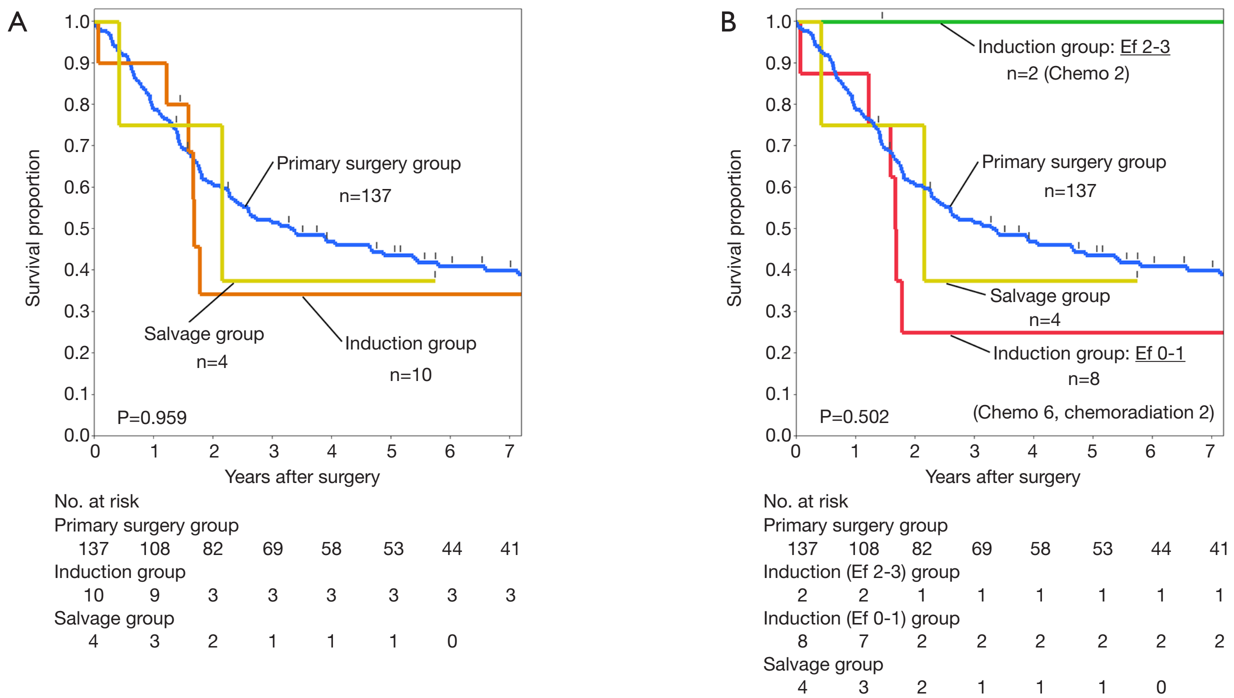

Figure 1 The prognostic outcomes of all patients who underwent pneumonectomy stratified based on therapeutic strategy (A) and further stratified by considering the pathological effects of induction therapy (B).

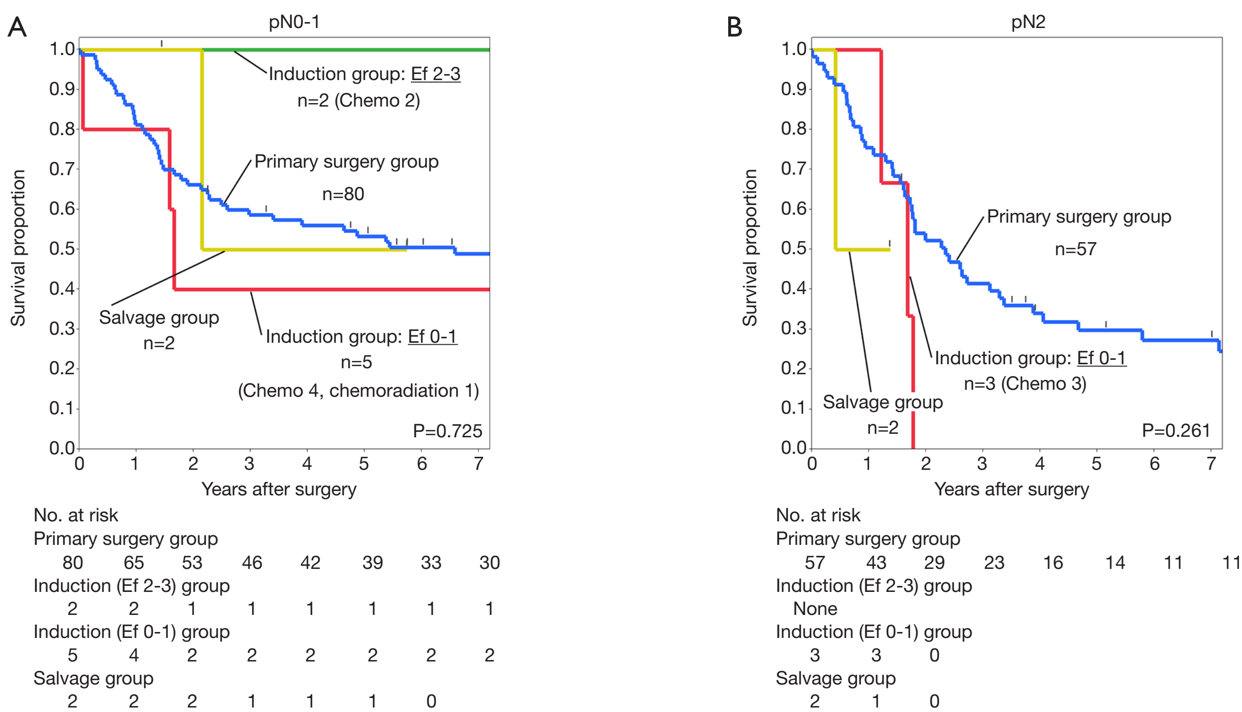

Figure 2 The prognostic outcomes of all patients who underwent pneumonectomy stratified based on the combination of therapeutic conditions, the pN status [pN0–1 (A) and pN2 (B)], and the pathological effects of the induction therapy.

reportedly include completeness of resection, presence or absence of mediastinal lymph node metastasis, and disease stage (13,14). Alexiou *et al.* summarized 206 pneumonectomies and reported that prognosis was poor in elderly patients and in those with a higher pathological stage, resulting in an operative mortality of 6.8% (13). Similarly, Licker *et al.* analyzed 193 pneumonectomies and reported 9.3% mortality within 30 postoperative days (14). In the present investigation, based on a similar sample size of patients, mortality within 30 postoperative days and that after 30 postoperative days but within 90 days was observed in 1.5% and 3.6% patients, respectively, in the primary pneumonectomy group.

Furthermore, we found that the prognostic outcome of pneumonectomy differs substantially based on the degree of invasion of neighboring organs. In cases with no invasion or infiltration only to the main bronchus or pleura, the outcome was significantly better than that in cases with the invasion of other deeper structures. As reported previously on the tumor invasion of neighboring organs (11,15), the invasion status of patients undergoing pneumonectomy may be a significant prognostic factor following completeness of resection, perhaps more significant than the presence or absence of mediastinal lymph node metastasis (*Table 2*).

The therapeutic strategy of performing pneumonectomy after induction therapy has revealed conflicting results. Martin *et al.* examined cases of various lung resection after induction therapy, including those who underwent pneumonectomy, and reported a mortality rate of 23.9% (11/46) following right pneumonectomy and an overall mortality of 11.3% (11/97) (16). Weder *et al.* reported excellent outcomes in 176 patients treated with pneumonectomy after induction therapy (chemotherapy, 20%; chemoradiotherapy, 80%) whereby the incidence of major complications was 13%, the 3-year OS rate was 43%, and the 5-year OS rate was 38% (4). In contrast, Albain *et al.* reported worse outcomes in patients treated with pneumonectomy than in those treated with radical chemoradiotherapy in a phase III study on chemotherapy plus radiotherapy followed by surgery in patients with IIIA-N2 lung cancer, leading to the conclusion that pneumonectomy cannot be recommended for these patients (3).

The choice between chemoradiotherapy and chemotherapy as induction treatment and the method to manage the radiotherapy dose have been controversial. Daly *et al.* reported a 5-year OS rate of only 33%, with no increase in the risk of mortality with right pneumonectomy in patients who underwent pneumonectomy (right, 18 patients; left, 12 patients) after high-dose radiation and concurrent chemotherapy; serious complications occurred in five patients, with perioperative deaths in four who underwent left pneumonectomy (17). Sonett *et al.* reported that a complete pathological response was achieved in 48% patients [lobectomy, 29 patients; pneumonectomy, 11 (right, 7; left, 4) patients] after high-dose radiation exceeding a dose of 59 Gy was given with concurrent chemotherapy (18). The authors emphasized that although surgery after high-dose radiation resulted in positive outcomes, bronchopleural fistulas can often form in patients with an uncovered bronchial stump and the incidence of complications can increase when using this therapeutic strategy in practice.

Conversely, it was claimed that radiotherapy did not have any additive effects on induction therapy in IIIA-N2 lung cancer (19-21). For 232 patients with IIIA-N2 lung cancer, Pless *et al.* compared surgery after induction chemoradiotherapy (117 patients including 25 who underwent pneumonectomy) with that after induction chemotherapy (115 patients including 19 who underwent pneumonectomy) and stated that one definitive local treatment modality combined with neoadjuvant chemotherapy was adequate to treat resectable stage IIIA-N2 non-small cell lung cancer (19). In a retrospective analysis conducted using the National Cancer Database that compared surgery after induction chemotherapy (528 patients including 83 who underwent pneumonectomy) and surgery after induction chemoradiotherapy (834 patients including 168 who underwent pneumonectomy), Yang *et al.* showed the non-inferiority of chemotherapy to chemoradiotherapy in terms of OS (20), and Shah *et al.* reported similar results in their meta-analysis (21).

Alternatively, very few reports have discussed salvage resection, and none have focused on salvage pneumonectomy. Bauman *et al.* examined the prognosis of 24 cases of salvage lung resection (including 10 cases of pneumonectomy) and stated that PET was effective for salvage surgery (5); this finding corroborated those reported by Schreiner *et al.*, who reviewed nine recent salvage lung resection reports including some by Bauman *et al.* and concurred with the overall effectiveness of salvage resection (6). However, these reviews focused mainly on cases of salvage resection after stereotactic radiotherapy. In Japan, Uramoto *et al.* reported eight cases of salvage surgery, including one case of pneumonectomy (7). In the present cohort, no patient with pN2 disease treated with salvage pneumonectomy survived for 2 years postoperatively, indicating that when considering salvage pneumonectomy, it is crucial to proactively diagnose mediastinal lymph node

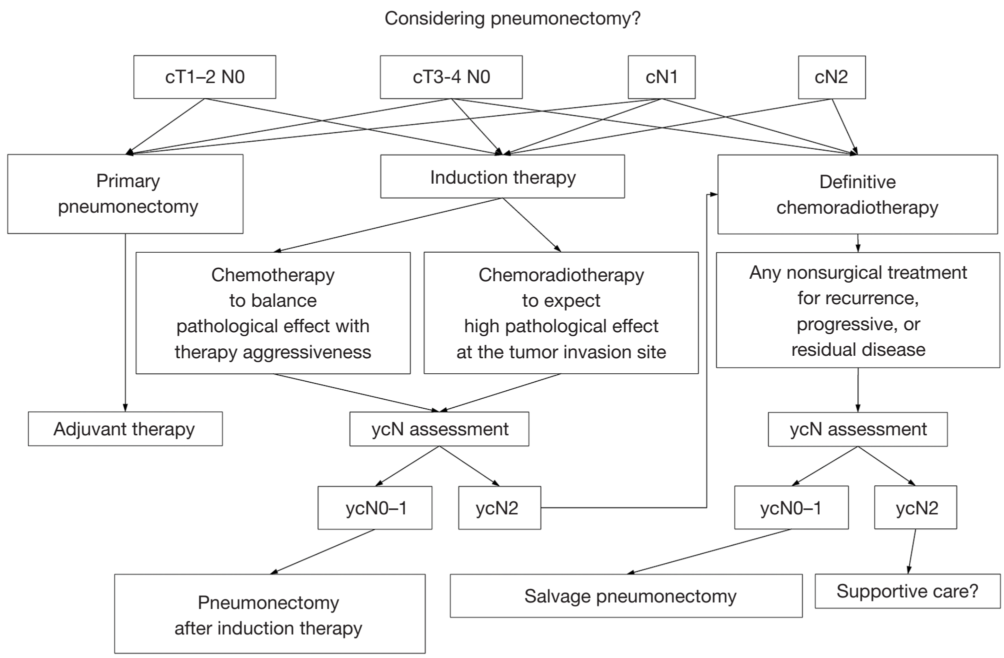

Figure 3 Possible treatment flows in our daily practice for a disease condition that could be considered for pneumonectomy. Details are discussed in the text.

metastasis preoperatively. Nevertheless, in critical situations wherein salvage surgery could be the only therapeutic choice, a decision to perform it on a case-by-case basis should be taken; if N2-positive lymph nodes are found, salvage surgery can be avoided or attempted despite poor prognosis because there are no other therapeutic options.

A review of all cases including the present investigation raises an important question of how to establish a daily clinical practice concerning pneumonectomy. *Figure 3* shows the possible treatment strategy in our daily practice for patients who could be treated with pneumonectomy. Whether to use only chemotherapy while placing importance on the significance of induction therapy as a systemic treatment or to use chemoradiotherapy while aiming to obtain higher histological effect at the surgical site is a difficult decision. Obtaining better histological effects should be balanced with surgical aggressiveness. In daily practice, we prefer chemotherapy over chemoradiotherapy for induction treatment to surgery, particularly when pneumonectomy is considered for the following reasons: (I) if only chemotherapy is used as a neoadjuvant treatment, postoperative radical radiation dose can be adjusted according to disease progression or when irradiation becomes necessary; (II) some reports suggest that combining radiation with preoperative treatment is not effective regardless of the disease condition (cN1 or cN2) (19-21); (III) surgery may be generally more difficult, and more complications may occur after induction chemoradiotherapy than after induction chemotherapy (16-18); (IV) induction chemotherapy could lead to downstaging, making it possible to avoid pneumonectomy (19-21); however, this treatment strategy may not necessarily be effective and a surgery-first strategy may suffice for the cN1 disease condition (22); and (V) postoperative adjuvant chemotherapy is more difficult after pneumonectomy than after lobectomy; therefore, chemotherapy could be performed preoperatively. In the induction group in this study, as high Ef. tended to be attained in patients with well-differentiated cancer and Ef. tended to be low in patients with poorly differentiated to undifferentiated cancer, the histological differentiation of the tumor may be a factor that predicts the reaction to induction therapy (detailed data were not shown).

This study has many limitations. One consideration regarding the experimental design of this investigation is the small sample size of patients treated with pneumonectomy after induction therapy or salvage pneumonectomy compared with the more rigorous and extensive reports in the literature cited above. A retrospective analysis of data from a single institution and a long surveillance period also limit generalization of the present findings. Considering the recent advances in molecular targeted therapies and immune checkpoint inhibitors, the relevance of the findings may be outdated. However, the study objective was to compare the outcomes of rarely performed pneumonectomy after induction therapy and even rarely performed salvage pneumonectomy with primary pneumonectomy, which enables a comprehensive understanding of practical pneumonectomies performed at a cancer center in Japan.

The outcomes of pneumonectomy differ considerably when there is an absence of invasion of neighboring organs or infiltration only to the main bronchus or pleura, and when there is an invasion of other deeper structures. Despite being performed after radical chemoradiotherapy, salvage pneumonectomy was easier to perform with fewer severe complications than pneumonectomy after induction therapy. With pN2 disease, the 2-year survival seemed to be difficult to achieve in patients who experienced pneumonectomy in the induction and salvage settings. It could be speculated that when considering pneumonectomy, it is essential to balance the pursuit of histological effects with treatment aggressiveness in induction settings and to strictly select patients with pN0–1 disease for salvage settings.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.03.19). YS serves as the unpaid editorial board member of *Journal of Thoracic Disease* from Aug 2019 to Jul 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of the Aichi Cancer Center Hospital (approval no. 2017-1-330). Informed consent was obtained from each patient for the use of clinical data for various studies.

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