ORIGINAL ARTICLE

Long-term survival in locally advanced non-small cell lung cancer invading the great vessels and heart

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Abstract

Background: The aim of this study was to analyze the surgical outcomes of locally advanced lung cancer invading the great vessels or heart, according to the extension of cancer invasion.

Methods: From 1995 to 2015, 59 patients who were surgically treated and pathologically diagnosed with T4N0–1 non-small cell lung cancer with invasion to the great vessels or heart were enrolled. Surgical outcomes were compared between patient groups with and without intrapericardial invasion.

Results: The median age was 64 years (interquartile range [IQR] 57–68) and 56 patients (95%) were male. In-hospital mortality was 9% and median overall survival was 30 months (IQR 12–83). One and five-year overall survival rates were 75% and 44%, respectively. The median overall survival in patients with lung cancer invasion to the intrapericardial space (n = 45) was 27 months (IQR 10–63), while it was 42 months (IQR 18–104) in patients without intrapericardial invasion (n = 14). Median disease-free survival was significantly poorer in patients with intrapericardial invasion (12 months; IQR 6–55), especially in patients with heart invasion (n = 11, 7 months, IQR 5–27), than in patients without intrapericardial invasion (30 months, IQR 13–103).

Conclusion: Patients with lung cancer invading the intrapericardial space showed worse surgical outcomes in both overall and disease-free survival. Therefore, surgical management should be carefully considered in patients with intrapericardial invasion.

Introduction

Even without distant metastasis, lung cancer can be a devastating disease, especially when it invades neighboring structures. The role of surgical resection for locally advanced non-small cell lung cancer (NSCLC) has been debated, particularly in regard to lung cancer invasion into the great vessels and heart, which was considered unresectable or was a relative contraindication for surgery.[1,2] However, recent studies have reported acceptable short and long-term outcomes in selected patients.[3,4] Therefore, it is important to clarify which patients can benefit from surgery according to the invasion site.

The American Joint Committee on Cancer (AJCC) cancer staging classifies invasion of the intrapericardial pulmonary vessels, superior vena cava (SVC), aorta, or heart in the same group, T4.[5] Furthermore, in the latest version of the National Comprehensive Cancer Network (NCCN) guidelines, surgery followed by chemotherapy with or without radiation therapy is highly recommended if the tumor is resectable, regardless of invading sites and extension.[6] In this study, we retrospectively analyzed long-term outcomes according to the presence of intrapericardial invasion in patients who underwent surgical resection of NSCLC with great vessel and heart invasion for curative

intent and were pathologically diagnosed as stage T4N0–1M0.

Methods

Patient selection

This was a retrospective study performed in a single center and approved by the hospital's institutional review board. From September 1995 to October 2015, 227 patients were surgically treated with curative intent for primary lung cancer and pathologically diagnosed with T4 NSCLC. Patients with N2–3 disease (n = 54), a previous history of other malignancy (n = 18), or who had received neoadjuvant treatment (n = 39) were excluded from the study. Patients with a Pancoast tumor; a multifocal T4 tumor; or other structural invasion to the trachea, carina, esophagus, or vertebrae were also excluded (n = 57). Other T4 lesions that invaded the mediastinum and recurrent laryngeal nerve were included. A total of 59 patients were enrolled and data on clinical, surgical, and pathologic characteristics were collected. Pulmonary artery invasion was defined as direct invasion of the tumor to the main trunk of the pulmonary artery, or pulmonary vein invasion as direct invasion of the intrapericardial part of the pulmonary vein. Heart invasion was defined as tumor involvement to the cardiac muscle, as revealed by pathologic reports, and all cases in this study were left atrial invasion. Invasion to the pulmonary artery, vein, and heart was classified as intrapericardial invasion.

Surgical procedures and follow-up

Pneumonectomy was performed in 31 patients (52.5%), bilobectomy in four (6.8%), and lobectomy in 24 (40.7%). Bronchial sleeve resection was required in eight patients (7 lobectomies and 1 pneumonectomy). Mediastinal lymph nodes were fully dissected in every case and the median number of total dissected lymph nodes was 21 (interquartile range [IQR] 14–31). After surgery, adjuvant chemotherapy was recommended for all patients, but only 36 patients (61%) were able to receive adjuvant treatments, including chemotherapy (n = 13), radiotherapy (n = 13), or both (n = 10). After discharge, patients visited the outpatient clinic and underwent computed tomography (CT) or positron emission tomography-CT (PET-CT) every three or four months for two years after the surgery and then every six months for the next three years. Patients visited the hospital annually for five years after the initial operation. The median follow-up period was 30 months (IQR 11.9–83.1). The end date for overall survival (OS) was defined as the date of the last follow-up or death. Disease-free survival (DFS) was defined as the interval from surgery to the first interpretation of recurrence, observed by imaging. Our hospital (n = 15) or National Cancer Registration Statistics (n = 25) confirmed the date of death for patients who had died during the follow-up period. Most of the living patients were followed-up in our outpatient clinic (n = 16). Telephone interviews were conducted to determine late outcomes in cases lost to follow-up.

Statistical analysis

All data were statistically analyzed using Stata version 10 (StataCorp LP, College Station, TX, USA). The in-hospital mortality and associated risk factors were evaluated by logistic regression. Univariate and multivariate survival analysis with Kaplan–Meier and Cox hazard modeling was calculated for OS and DFS rates, and also for cumulative recurrence rate. Variables correlated at $P < 0.20$ in univariate analysis were included in multivariate analysis. Analyzed predictors and risk factors were regarded as significant in accordance with the ratio formula when $P < 0.05$.

Results

Patient characteristics

The median age was 64 years (IQR 57–68) and 56 patients (94.9%) were male. Fifty-five patients (93.2%) had a smoking history. Squamous cell carcinoma (n = 37, 62.7%) was the most frequent histologic subtype, followed by adenocarcinoma (20.3%), large cell neuroendocrine carcinoma (3.4%), and other subtypes (13.6%). Local lymph node metastasis (N1) was present in 32 patients (54.2%) and the median number of positive lymph nodes was 2 (IQR 1–2). Structural involvement included the left atrium (n = 11, 18.6%), aorta (n = 12, 20.3%), superior vena cava (n = 10, 17%), main pulmonary artery (n = 31, 52.5%), and intrapericardial pulmonary vein (n = 21, 35.6%). Forty-five patients (76.3%) had lung cancer invasion to the intrapericardial space, while 14 patients (23.7%) had no intrapericardial extension. Seven patients (11.9%) underwent tumor resection under cardio-pulmonary bypass (CPB) as a result of invasion into the aorta (n = 4), left atrium (n = 2), and main pulmonary artery (n = 1). Right-sided tumors more frequently involved the left atrium than left-sided tumors (29.2% vs. 11.4%; P = 0.086). On the other hand, main pulmonary artery involvement was significantly more frequent in left-sided tumors (71.4% vs. 25%; $P < 0.001$). Complete resection was achieved in 51 patients (86.4%). Two patients had grossly residual tumors (R2) that both encircled the aortic branch vessels in the early period of the study. The other six patients had microscopic residual tumors (R1) in the resection margin: three patients in the

contralateral pulmonary artery after angioplasty of the main pulmonary artery, and one patient in the left atrium. There was no significant difference in the proportion of incomplete resections between the heart and other invasion sites ($P = 0.777$). After surgery, the eight patients with incomplete resection received adjuvant chemotherapy ($n = 6$) or radiation therapy ($n = 2$).

Short-term results

In-hospital mortality was 6.8% ($n = 4$) and the cause of the death was acute respiratory distress syndrome in all patients. All in-hospital mortalities occurred in patients with intrapericardial invasion, but this result was not statistically significant ($P = 0.248$). Pneumonectomy seemed to increase the risk of in-hospital mortality in univariate analysis ($P = 0.049$); however, multivariate analysis showed no significance. Surgical findings of left atrial invasion or CPB application during surgery also did not increase in-hospital mortality. In the first half of the study from 1995 to 2005 ($n = 22$), CPB was performed in only one patient and patients with grossly remnant tumors were included in this period. All of the in-hospital mortalities were observed during this period. Tumor resection under CPB was performed more frequently in the later half of the study ($n = 4$) and neither in-hospital mortality nor grossly remnant tumors occurred (Table 1).

Long-term survival and prognostic factors

The median OS was 30 months (IQR 11.9–83.1), the one-year OS rate was 74.6%, and the five-year OS rate was 43.8%. In patients with lung cancer invasion to the intrapericardial space, the median OS was 26.5 months (IQR 9.8–62.8), while it was 42.4 months (IQR 18.1–103.5) in patients without intrapericardial invasion. In univariate analysis, older age, pneumonectomy, incomplete resection, histopathologic type of large cell neuroendocrine carcinoma, right-sided tumor location, intrapericardial invasion, and absence of adjuvant chemotherapy showed statistical significance ($P < 0.20$). However, there was no significant relationship with smoking, bronchial sleeve resection, CPB, number of metastatic lymph nodes, total number of dissected lymph nodes, histologic differentiation, or adjuvant radiotherapy ($P > 0.20$). In multivariate analysis, independent predictors of OS were completeness of resection ($P = 0.048$), histopathologic type ($P = 0.002$), location of tumor ($P = 0.001$), intrapericardial invasion ($P = 0.037$), and adjuvant chemotherapy ($P = 0.039$) (Table 2, Fig 1).

The median DFS was 15.5 months (IQR 16.4–62.8), the one-year DFS rate was 57.6%, and the five-year DFS rate was 36.4%. The median DFS was shorter in patients with

Table 1 Clinicopathologic features, surgical procedures, and adjuvant treatments

Clinicopathologic features	
Age, years, median (IQR)	64 (57–68)
Gender, male (%)	56 (95)
Smoking history (%)	55 (93)
Histologic subtype (%)	
Squamous cell carcinoma	37 (63)
Adenocarcinoma	12 (20)
Large cell neuroendocrine carcinoma	2 (3)
Other	8 (14)
N1 disease (%)	32 (54)
Number of positive LN, median (IQR)	2 (1–2)
Number of dissected LN, median (IQR)	21 (14–31)
Structural involvement (%)	
Left atrium	11 (19)
Aorta	12 (20)
Superior vena cava	10 (17)
Main pulmonary artery	31 (53)
Intra-pericardial pulmonary vein	21 (36)
Intra-pericardial involvement (%)	45 (76)
Tumor location, left thorax (%)	35 (59)
Surgical procedures	
Pulmonary resection (%)	
Pneumonectomy	31 (52)
Bi-lobectomy	4 (7)
Lobectomy	24 (41)
Bronchial sleeve resection (%)	8 (14)
Cardio-pulmonary bypass (%)	7 (12)
Incomplete resection (%)	8 (14)
Grossly residual tumor	2 (3)
Microscopic residual tumor	6 (11)
Adjuvant treatments	
Chemotherapy (%)	13 (22)
Radiotherapy (%)	13 (22)
Both (%)	10 (17)

IQR, interquartile range; LN, lymph node.

lung cancer invasion to the intrapericardial space (12.5 months, IQR 6.3–55.4), especially in patients with left atrial invasion ($n = 11$, 7.1 months, IQR 4.7–26.5), than in patients without invasion (29.6 months, IQR 12.9–102.9). In univariate analysis of DFS, age, histopathologic type, location of tumor, number of metastatic lymph nodes, intrapericardial invasion, and adjuvant chemotherapy showed statistical significance ($P < 0.20$). In multivariate analysis, independent predictors of DFS were histopathologic type ($P = 0.004$), tumor location ($P < 0.001$), number of metastatic lymph nodes ($P = 0.001$), and adjuvant chemotherapy ($P = 0.011$) (Table 2, Fig 2). Intrapericardial invasion showed borderline significance ($P = 0.057$) for DFS.

During the follow-up period, 24 patients suffered from cancer recurrence. Of these patients, 10 experienced locoregional recurrence at the bronchial stump site ($n = 5$), mediastinal lymph nodes ($n = 2$), chest wall ($n = 2$), and

Table 2 Risk factors for overall and disease-free survival

| Factors | Overall survival | | | Disease-free survival | | |
| | Univariate | Multivariate | | Univariate | Multivariate | |
	P	*P*	95% CI	*P*	*P*	95% CI
Age	0.020	—	—	0.107	—	—
Pneumonectomy	0.122	—	—	—	—	—
Complete resection	0.184	—	—	—	—	—
R0	—	—	—	—	—	—
R1	—	—	—	—	—	—
R2	—	0.048	1.01–24.8	—	—	—
Histologic type	0.002		—	0.007		—
SCC	—	—	—	—	—	—
ADC	—		—	—	—	—
LCNC	—	0.002	2.74–84.8	—	0.004	2.09–53.4
Other	—	—	—	—	—	—
Intra-pericardial invasion	0.192	0.037	1.07–7.76	0.137	—	—
Tumor location, left	0.054	0.001	0.09–0.56	0.070	< 0.001	0.12–0.55
Adjuvant chemotherapy	0.013	0.039	0.16–0.95	0.067	0.011	0.17–0.79
Number of metastatic LNs	—	—	—	0.046	0.001	1.25–2.22

ADC, adenocarcinoma; CI, confidence interval; LCNC, large neuroendocrine carcinoma; LNs, lymph nodes; R0, complete resection; R1, microscopic residual tumor; R2, grossly residual tumor; SCC, squamous cell carcinoma.

ipsilateral lung (*n* = 1). The remaining 14 patients developed distant metastasis at the initial recurrent site. Three of the six patients who had microscopic incomplete resection suffered from cancer recurrence (1 local, 2 distal). The median interval to recurrence was 10.6 months (IQR 6.3–13.3). The cumulative recurrence rate within two years was 41.3% and 49.3% within five years. The significant risk factors in multivariate analysis for cumulative recurrence rate were histopathologic type (*P* = 0.014) and left atrial invasion (*P* = 0.012). There was no statistical significance in multivariate analysis (*P* = 0.056), but only two patients (16.7%) with aortic invasion who also had left atrial invasion showed distant recurrence during follow-up (Fig 3).

Discussion

In patients with stage IIIA disease without mediastinal lymph node metastasis, complete resection of a locally advanced tumor is the most important procedure to improve long-term survival, thus is recommended as an initial treatment.[7–10] In the NCCN guidelines (version 8.2017) for NSCLC, complete resection of a tumor followed by chemotherapy is recommended for patients with resectable T4 disease.[6] T4 lung cancer consists of various disease conditions based on the organs involved, including the carina/trachea, esophagus, vertebrae, and great vessels and heart, and shows different long-term outcomes according to invasion site.[11] Recent studies have reported improvement in the five-year OS rates of lung cancer invading the trachea or carina to 51–70% after surgery.[12–16] A superior sulcus tumor, which is also referred to as a

Pancoast tumor, has a 33–56% five-year OS rate.[17–19] Diaphragm invasion, newly classified as T4 disease in the eighth edition of AJCC lung cancer staging, showed five-year OS of 43% (55% for N0 disease) after complete resection.[5,20] However, lung cancer invading the cardiovascular system still has a poorer long-term outcome than other T4 lesions. Five-year OS rates of lung cancer with SVC invasion have been reported at 24–31%,[12,21,22] 17–48% with aortic invasion,[3,4,23,24] and 14–30% with left atrial invasion.[25–27]

Superior vena cava invasion of lung cancer has been a contraindication for surgery; however, several studies have shown improved results with acceptable long-term outcomes.[12,21,22] Suzuki *et al.* reported that five-year OS was significantly higher in patients with SVC invasion by direct tumor extension than by metastatic nodes (36% vs. 6.6; *P* = 0.05) and commented that SVC invasion by metastatic lymph nodes was a significantly poor prognostic factor.[21] Spaggiari *et al.* reviewed 52 patients with lung cancer invading the SVC, and reported five-year OS of 31%, with long-term results affected by nodal stage (52% in N0/N1 disease, 21% in N2 disease).[22] In our study, 10 patients had SVC involvement and their five-year OS was 47%.

Lung cancer with aortic invasion had also been considered inoperable; however, a few recent studies have shown encouraging long-term results with radical resection in selected patients. Ohta *et al.* performed extensive resection of lung cancer invading the aorta, and reported five-year OS of 48%, with a significantly higher survival rate in N0 patients (70%; *P* = 0.007).[4] In another study of lung cancer with aortic invasion (*n* = 13) conducted by Wex *et al.*, aortic resection and reconstruction showed
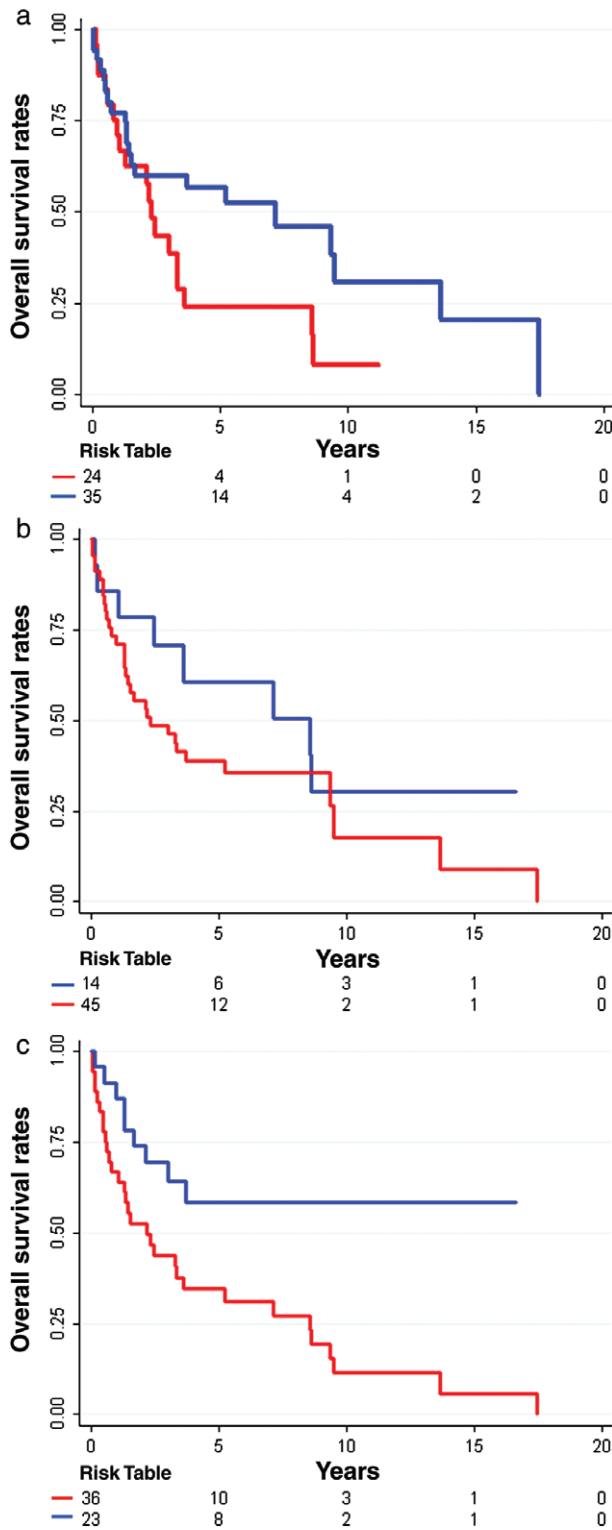
Figure 1 Kaplan–Meier overall survival curve according to tumor location: (**a**) (——) left-side cancer, and (——) right-side cancer, intrapericardial invasion; (**b**) (——) no intrapericardial invasion, and (——) with intrapericardial invasion, and adjuvant chemotherapy; (**c**) (——) adjuvant chemotherapy, and (——) no adjuvant chemotherapy.
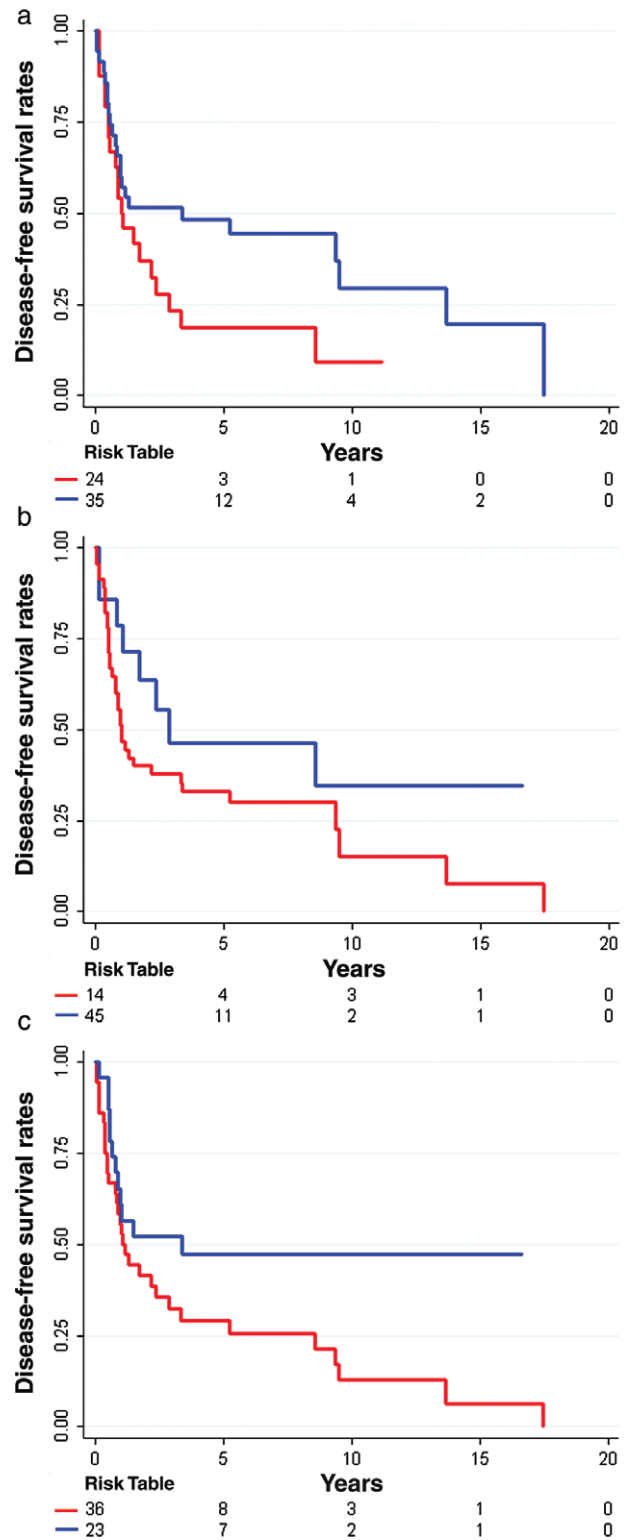
Figure 2 Kaplan–Meier overall survival curve according to the location of the tumor: (**a**) (——) left-side cancer, and (——) right-side cancer, intrapericardial invasion; (**b**) (——) no intrapericardial invasion, and (——) with intrapericardial invasion, and adjuvant chemotherapy; (**c**) (——) adjuvant chemotherapy, and (——) no adjuvant chemotherapy.
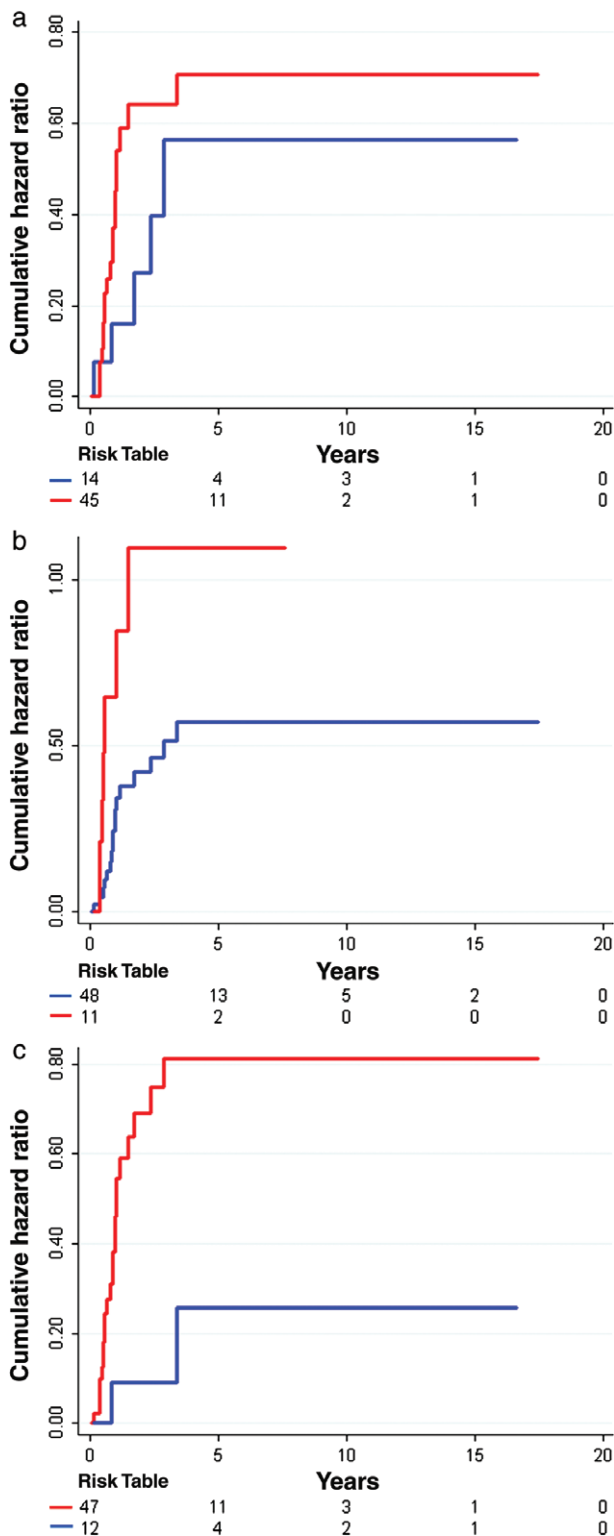
Figure 3 Nelson–Aalen cumulative hazard curves according to intra-pericardial invasion: (**a**) (———) no intra-pericardial invasion, and (———) with intra-pericardial invasion, left atrial invasion; (**b**) (———) left atrial invasion, and (———) other sites and aortic invasion; (**c**) (———) aortic invasion, and (———) other sites.

better outcomes than subadventitial dissection.[3] In our study, 12 patients underwent radical resection for lung cancer invasion to the aorta, and the five-year OS of these patients was 75%. Two patients who also had left atrial invasion and received grossly incomplete resection in the early period of this study suffered tumor recurrence. The five-year OS of four patients who had solely aortic invasion was 100% without cancer recurrence. Fourteen patients with lung cancer invasion limited to the aorta or SVC and had no intrapericardial invasion, showed significantly better OS ($P = 0.037$), and borderline significance in DFS ($P = 0.057$). Therefore, although the evidence is limited, we might expect better long-term outcomes from surgery in locally advanced lung cancer patients without intrapericardial invasion.

On the other hand, lung cancer with left atrial invasion has shown poor long-term results. Fukuse *et al.* reported in 1995 that patients with great vessel involvement had significantly better outcomes than those with left atrial invasion (median survival time 19 vs. 10 months; $P = 0.036$).[28] In recent studies, these surgical outcomes were not improved in patients with left atrial invasion. In a study conducted by Stella *et al.*, the five-year survival rate of lung cancer with atrial invasion was 30%, with the main cause of death being systemic recurrence.[25] In our study, 11 patients had left atrial invasion and one patient had a microscopic residual tumor. There was no in-hospital mortality, but the five-year overall survival rate was relatively lower (21%) and the recurrence rate significantly higher ($P = 0.012$) than in other invasion sites. Former studies of initial surgery for atrial invasion have shown poor long-term results; therefore, neoadjuvant treatment in such cases has recently been reported.[29–31] Shien *et al.* performed neoadjuvant treatment for locally advanced lung cancer (clinical stage T3–4N0–1), and reported that the clinical neoadjuvant group achieved significantly better overall survival than the surgery-first group ($P = 0.0027$).[29] However, according to the NCCN guidelines (version 8.2017), surgery is recommended as initial treatment for resectable T4N0–1 disease, except for superior sulcus tumors.[6] Further evaluation is required, which may involve extending the criteria for applying neoadjuvant treatment in locally advanced lung cancer.

Differences in long-term survival according to the site of involvement could be affected by the completeness of resection, thought to be essential for better prognosis. Shiraishi *et al.* conducted a study of 16 patients with aortic involvement, and reported significant differences in five-year overall survival between complete ($n = 8$) and incomplete ($n = 8$) resection groups.[23] The incomplete resections primarily resulted from the patients' poor preoperative condition, which subsequently prevented CPB. Langer *et al.* performed a comparison analysis of patients with T4

lung cancer who underwent surgery with or without CPB and found no statistical difference in OS or DFS between the no CPB and CPB groups (*P* = 0.89 and *P* = 0.88, respectively).[32] In our study, incomplete resection, especially with grossly remnant tumor (R2), was an independent risk factor for OS (*P* = 0.048). Despite concerns of intolerance of CPB during pulmonary resection, CPB did not increase postoperative complications or in-hospital mortality. As such, applying CPB to achieve complete resection should not be avoided. Muralidaran *et al.* performed a systematic review of published studies of locally advanced lung cancer surgery under CPB and reported 30-day and 90-day mortalities of 0% and 1%, finding that an unplanned bypass was a significant prognostic factor for a poorer outcome.[33] In patients assessed as unable to tolerate CPB, an alternative surgical option to achieve complete resection could be increasing the length of the atrial cuff by interatrial septum dissection.

A limitation of this study is that only a small number of patients for each group were retrospectively evaluated. However, only pathologically diagnosed T4N0–1 patients were included, and patients who underwent neoadjuvant treatments and with other T4 lesions were excluded to confirm the role played by surgery according to the site of invasion. Another limitation of this study is associated with the exclusion of patients who underwent neoadjuvant treatment, which might be a critical issue in locally advanced lung cancer. Nevertheless, an attempt was made to clarify which subgroup would benefit most from radical surgery as an initial treatment. In this study, patients with locally advanced lung cancer without intrapericardial invasion showed promising results after surgery, without induction treatments. However, further studies including comparative analysis according to neoadjuvant treatments are necessary in subgroups with or without intrapericardial invasion.

In conclusion, the presence of intrapericardial invasion is an independent predictor of long-term survival in lung cancer patients with invasion to the great vessels and heart. Patients who did not develop intrapericardial invasion showed encouraging long-term outcomes, which suggests that extensive resection is a feasible treatment option in this group. However, patients with lung cancer invading the intrapericardial space showed poor OS and DFS outcomes; therefore, further studies of other treatment strategies, including chemoradiation therapy in neoadjuvant form, should be performed in the future.

Disclosure

No authors report any conflict no of interest.

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