Assessing the prognostic impact of the International Association for the Study of Lung Cancer proposed definitions of complete, uncertain, and incomplete resection in non-small cell lung cancer surgery

ABSTRACT

Objective: The aim of this study was to assess the prognostic impact of the definitions of complete, uncertain, and incomplete resection in non-small cell lung cancer (NSCLC) surgery, as proposed by the International Association for the Study of Lung Cancer (IASLC).

Patients and methods: Single institution retrospective study of consecutive patients undergoing surgery for NSCLC between 1998 and 2007. Complete resection was defined by absence of gross and microscopic residual disease; systematic nodal dissection; no extracapsular extension in distal lymph nodes; and negativity of the highest mediastinal node removed. An uncertain resection was defined by free resection margins, but one of the following applied: lymph node evaluation less rigorous than systematic nodal dissection; positivity of the highest mediastinal node removed; presence of carcinoma in situ at the bronchial margin; positive pleural lavage cytology. A resection was defined incomplete by presence of residual disease; extracapsular extension in distal lymph nodes; positive cytology of pleural or pericardial effusions. Follow-up was complete and all patients were followed up until death or for a minimum period of 5 years. Overall survival (OS) was analyzed using Kaplan-Meier method, log rank test, and Cox proportional hazards model.

Results: A total of 1277 patients were identified. One thousand and three patients (78.5%) underwent complete resection, 185 (14.5%) underwent uncertain resection, and 89 (7.0%) underwent incomplete resection. Both uncertain and incomplete resection were associated with significantly worse OS when compared with complete resection (hazard ratio: 1.69 and 3.18, respectively; both p=0.0001). Median OS and 5-year survival rate were 80.1, 39.9, 17.3 months and 58.8%, 37.3%, 15.7% in patients undergoing complete, uncertain, and incomplete resection, respectively.

Conclusion: The present analysis suggests that in patients undergoing surgery for NSCLC, the IASLC definitions of complete, uncertain, and incomplete resection are associated with statistically significant differences in survival.

KEYWORDS

Non-small cell lung cancer; Surgery; Incomplete resection; Residual disease; Survival.

1. Introduction

In patients with non-small cell lung cancer (NSCLC), in the absence of distant metastasis, complete surgical resection continues to be the mainstay therapeutic modality. However, controversy exists about the definition of complete resection in NSCLC surgery [1-4] and inconsistencies regarding the impact of incomplete resection on prognosis further complicate matters [5-7]. In 2005, the International Association for the Study of Lung Cancer (IASLC) proposed several criteria to define complete and incomplete resection in NSCLC surgery taking into account pertinent literature and incorporating the concept of systematic nodal dissection [8]. Besides, a third category of uncertain resection was added.

To our knowledge, no studies have specifically addressed the prognostic significance of the IASLC proposed definitions. Thus, we conducted a retrospective study evaluating the prognostic impact of these definitions in conjunction with other established clinicopathologic prognostic factors in a series of 1277 consecutive patients undergoing surgery for NSCLC.

2. Patients and methods

2.1 Data retrieval

The study protocol was approved by the Institutional Review Board with a waiver of patient consent. We performed a retrospective analysis on a prospectively computerized database including all consecutive

NSCLC patients who underwent thoracotomy for a planned resection between January 1998 and December 2007 in our institution. The following exclusions were made: patients proved to have not resectable lesions at the time of exploration, and patients receiving pulmonary resection for carcinoid tumors.

2.2 Data variables

The demographic and clinical variables considered were patient age, patient gender, and comorbidity. The modified Charlson Comorbidity Index (CCI) [9] was used as a measure of comorbidity and each patient was categorized in one of three comorbidity grades: 0, 1-2, and 3 or more.

Treatment variables included induction therapy, year of surgery, surgery, and adjuvant therapy. Surgical procedures were defined as pneumonectomy, lobectomy, segmentectomy, and wedge resection. Bronchial sleeve resections and bilobectomies were grouped under the lobectomy category. Perioperative outcomes included length of hospital stay, postoperative morbidity and mortality. Overall postoperative morbidity was defined as the occurrence of at least one complication within 30 days after surgery or during the hospitalization. Major cardiopulmonary morbidity occurred if one or more than one of the following were present: acute myocardial infarction; cardiac failure requiring inotropic support; haemodynamically unstable arrhythmia requiring treatment; pulmonary embolism; adult respiratory distress syndrome; respiratory failure (PaO_2 <65 mmHg and/or $PaCO_2$ >45 mmHg); pneumonia defined by typical clinical, laboratory, and radiographic features; atelectasis requiring bronchoscopy; bronchopleural fistula. Operative mortality was reported as 30-day mortality, defined as any death occurring within 30 days of surgery; perioperative mortality, defined as any death occurring in hospital or within 30 days of surgery; and 90-day mortality, defined as any death occurring within 90 days of surgery.

Tumor variables considered were histology, tumor size, pT status, pN status, and pTNM stage. Histology subtypes were classified into categories of adenocarcinoma, squamous cell carcinoma, and other histologic types. Patients were initially staged according to the sixth TNM classification and the TNM

descriptors were converted to the eighth edition [10]. Intrathoracic lymph node stations were localized according to the Mountain-Dresler map [11].

Finally, operative notes and pathology reports were reviewed and the completeness of resection was determined based on the IASLC proposed criteria [8]. A complete resection required all of the following: absence of gross and microscopic residual disease; systematic nodal dissection including, at least, three nodes removed from pulmonary stations and three removed from mediastinal stations, one of which had to be the subcarinal station; no extracapsular extension in distal lymph nodes; and negativity of the highest mediastinal node removed. An uncertain resection was defined by free resection margins, but one of the following applied: lymph node evaluation less rigorous than systematic nodal dissection; positivity of the highest mediastinal node removed; presence of carcinoma in situ at the bronchial margin; positive pleural lavage cytology. A resection was defined incomplete if any of the following applied: presence of residual disease; extracapsular extension in distal lymph nodes; positive cytology of pleural or pericardial effusions.

2.3 Statistical methods

2.3.1 Sample size and power of the study

The power of the study associated with the available sample size was based on the primary endpoint of overall survival (OS) among patients undergoing complete resection in comparison with OS among patients undergoing uncertain or incomplete resection for NSCLC. For an α value equal to 0.05 level of significance, considering a total of 1277 available patients and an accrual time of 120 months, and assuming a median follow-up time of 66 months and median survival times m_1 = 75 months and m_2 = 57 months among patients undergoing complete resection and patients undergoing uncertain or incomplete resection, respectively (hazard ratio = 1.316), a power (1 - β) 92.4% was achieved. The power was estimated assuming a dropout rate ϕ equal to 0.20 (Schoenfeld's formula [12] implemented by the ADDPLAN version 4.0.3 [Adaptive Design and Analyses, ADDPLAN GmbH, Germany] software).

2.3.2 Statistical analysis

Descriptive statistics were used to describe patient characteristics, surgical treatment and perioperative outcomes, and tumor characteristics. Categorical data were reported as counts and proportions. After being examined for normality with the Shapiro-Wilk test, continuous data used in the study were not symmetrically distributed and were expressed as medians and interquartile ranges, unless otherwise stated. For between-group comparisons, we used the Kruskal-Wallis test for continuous data and the χ^2 test for categorical data. All variables entered in the study were complete.

The primary endpoint of interest was the impact of the IASLC definitions of complete, uncertain, and incomplete surgical resection on OS, calculated as the difference in months between date of surgery and death from any cause or censored at the date of last contact or the end of the study in September 2013. Follow-up was complete and all patients were followed up until death or for a minimum period of 5 years. Long-term mortality data were collected using a combination of data linkage to civil administrations or direct contact with patients. Survival curves were estimated using the Kaplan-Meier approach and differences between groups were analyzed using the log rank test. Cox proportional hazard regressions were used to estimate crude and adjusted hazard ratios for death and relative 95% confidence intervals in order to assess the significance of covariates included in the models. An α value equal to 0.05 was used for statistical significance.

Statistical analysis was performed using the IBM SPSS Statistics version 22 (IBM SPSS Inc., USA) software package.

3. Results

3.1 Patient data

A total of 1277 consecutive patients were included in the final analysis (Figure 1). One thousand and three patients (78.5%) underwent complete resection, 185 (14.5%) underwent uncertain resection, and 89 (7.0%) underwent incomplete resection. The uncertain resection group included 107 patients in whom lymph node evaluation was less rigorous than systematic nodal dissection; 76 patients in whom the highest mediastinal node removed was positive; and 5 patients in whom the bronchial resection margin showed carcinoma in situ. In 3 patients, the resection fulfilled more than one criteria required to be designated as an uncertain resection. As a matter of fact, during the study period, pleural lavage cytology was not performed. However, at thoracotomy, small amounts of pleural fluid (less than 100 ml) were observed in 125 (9.8%) patients out of 1277 and cytological examination results were positive for malignant cells in 14 (11.2%). These were included in the incomplete resection group (n=89) which also comprised 12 patients with macroscopic residual tumor (mediastinum 7, chest wall 5); 32 patients with microscopic residual tumor (bronchial stump 15, vascular stump 4, mediastinum 4, chest wall 9); and 41 patients with extracapsular nodal involvement. In 9 patients, the resection fulfilled more than one criteria required to be designated as an incomplete resection.

Baseline demographic and clinical variables, treatment variables, and tumor variables in the three study groups are summarized in Table 1. When comparing the three groups, there was no significant difference with regard to baseline demographic and clinical variables. However, several differences were identified in treatment and tumor variables. Patients undergoing uncertain or incomplete resection were more likely to have received induction therapy and to receive adjuvant therapy. In addition, there were significant differences between the groups in the types of surgery. Indeed, during the study period, sublobar resections were mainly used as a compromise procedure in patients deemed to be high surgical risk because of comorbidities or impaired cardiopulmonary function, and were associated with lower prevalence of systematic nodal dissection and higher prevalence of residual disease. The groups were otherwise similar for perioperative outcomes. As for tumor variables, patients undergoing complete resection were more likely to have a smaller tumor size and lower pathologic disease stage.

3.2 Survival data

At the conclusion of this study in September 2013, after a median follow-up of 66.8 months (IQR 21.3 to 102.5), 853 patients (66.8%) had died (median survival 32.1 months; range 0 to 188.6; IQR 14.9 to 67.5). Median follow-up of 424 surviving patients (33.2%) was 109.6 months (range 62.1 to 187.0; IQR 86.5 to 140.3).

From our Kaplan-Meier analysis, we found that complete resection was associated with significantly better OS compared with uncertain or incomplete resection (log rank p=0.0001) (Figure 2 and Table 2). More specifically, the 5-year survival rate among the 5 patients undergoing uncertain resection because of presence of carcinoma in situ in the bronchial resection margin was 40.0% while the 5-year survival rate was 28.8% and 44.2% in patients (n=76) in whom the highest mediastinal node removed was positive and in patients (n=107) who underwent less rigorous lymph node evaluation, respectively. Of note, all the 9 patients in whom the resection showed more than one of the characteristics required to be designated as an incomplete resection had died by the end of the second year. On the other hand, in the subset of 80 patients in whom the resection showed only one of the characteristics required to be designated as an incomplete resection, long-term (≥5 years) survivors included 3 (30.0%) of 10 patients with positive cytology of pleural fluid, 1 (11.1%) of 9 patients with macroscopic residual tumor, 6 (21.4%) of 28 patients with microscopic disease in a resected margin, and 4 (12.1%) of 33 patients with extracapsular nodal involvement.

Additional factors that were determined as significant at univariable analysis of survival included age, gender, CCI, occurrence of major postoperative cardiopulmonary complications, tumor size, pT status, pN status, pTNM stage, and administration of adjuvant therapy after surgery (Table 2).

At the multivariable analysis (Table 3), age, gender, CCI, completeness of resection, pT status, and pN status were the parameters that retained significant independent prognostic impact. The greatest hazard ratios of death were observed for incomplete resection (2.299 times more in respect to patients undergoing complete resection), for pT4 tumor (1.878 times as opposed to patients with pT1 tumor) and for pN2 disease (1.840 times as opposed to patients with pN0 disease).

Finally, in an effort to explore further the prognostic significance of the IASLC definitions, these patients were compared to patients (n=57) who, during the study period, were proved to have unresectable lesions at the time of exploration. Patients undergoing exploratory thoracotomy faced significantly worse survival than did patients undergoing incomplete resection: median OS and 5-year survival rate were 12.1 months (95% CI: 7.9-16.2) and 10.5%, respectively (p=0.0001).

4. Discussion

The aim of our study was to investigate whether the IASLC definitions of complete, uncertain and incomplete resection were able to predict OS in a population of patients undergoing surgery for NSCLC. Admittedly, the definition of complete resection in NSCLC surgery has markedly varied among reports. According to Mountain [2], an apparent complete resection is defined as follows: (1) the surgeon is certain that all known disease has been removed; (2) the resection margins are free at pathologic examination; (3) within each major lymphatic drainage region the most distal node is negative at microscopy; and (4) there is no extranodal extension in the resected mediastinal lymph nodes. On the other hand, Shields [4] emphasized the need to establish a stringent definition of an incomplete resection which was to be based on histological confirmation of residual disease at the margins of the resected specimen. However, Law and coworkers [13] had pointed out that the histological report of tumor at the margin of the resected bronchus may reflect sectioning artifacts while another interpretation problem was illustrated in a study on the reproducibility of intranodal and extranodal growth patterns in the histological examination of lymph nodes in NSCLC [14]. Indeed, Fujimoto and coworkers [15] described 26 patients with NSCLC who underwent completion pneumonectomy following incomplete initial resection due to pathologically proven positive bronchial margin (n=15) or positive N1 disease with extracapsular infiltration (n=11). The mean interval between first and second operation was 28 days and no residual tumor was found in 18 (69.2%) of 26 patients. Discordant definitions of complete resection [1-4], coupled with elusive identification of resection margins and

difficulties in the reproducibility of metastatic growth patterns in lymph nodes [13-15], may represent a plausible explanation of inconsistencies regarding the prognostic impact of an incomplete resection on survival [5-7].

The results from the current study indicate that complete resection was associated with significantly better survival compared with uncertain or incomplete resection, as defined according to the IASLC criteria. Furthermore, patients undergoing exploratory thoracotomy had significantly worse outcomes than those undergoing incomplete resection [16]. The data do emphasize the primary rule of achieving a complete resection in NSCLC surgery and imply that the IASLC definitions of uncertain and incomplete resection are markers of advanced loco-regional disease and higher likelihood of occult distant metastasis [17].

Residual disease was documented in 44 (3.4%) of 1277 patients, including 32 (2.5%) with microscopically positive margins and 12 (0.9%) with macroscopically positive margins. The incomplete resection group also included 14 patients with cytologically positive pleural fluid and 41 patients with extracapsular N2 disease. Considering that in 9 patients the resection fulfilled more than one of the criteria required to be designated as an incomplete resection, the overall prevalence of incompletely resected NSCLC in our study population (7.0%) is similar to that reported in two recent studies which have analyzed the U.S. National Cancer Data Base adopting the traditional criterion of margin positivity [18,19].

According to the IASLC definitions [8], the uncertain resection category includes cases in which there is no evidence of residual disease but the strict criteria of complete resection are not fulfilled. In the present series, the uncertain resection group comprehended 107 (8.4%) out of 1277 patients in whom lymph node evaluation was less rigorous than systematic nodal dissection, 76 (5.9%) patients in whom the highest mediastinal node removed was positive, and 5 (0.4%) patients in whom the bronchial resection margin showed carcinoma in situ. Although lymph node assessment is a prerequisite for accurate staging in NSCLC resection, the extent of lymph node removal required is controversial and the quality of lymph node examination is highly variable in clinical practice. Osarogiagbon and Yu [20], querying the U.S. Surveillance, Epidemiology, and End Results (SEER) database of lung cancer resections from 1998 to 2009, found that patients in whom no lymph nodes were examined (pNx) represented 13% of the whole surgical

resection cohort (including 51% of sublobar resections). Besides, more than 50% of NSCLC resections had suboptimal mediastinal lymph node examination [21]. As for the presence of metastasis to the highest mediastinal lymph node, in this study 76 (35.0%) of 217 patients with pN2 disease showed metastatic involvement in this location, which is lower than that observed by Zheng and coworkers (44.8%) [22].

Statistically significant differences were not observed between the three study groups in baseline demographic characteristics, whereas a marginal difference was seen in the CCI: the morbidity index score showed a slight increase in patients undergoing uncertain or incomplete resection as compared with patients undergoing complete resection. Most likely, this is due to two factors: limited lymph node examination or nonexamination, and unanticipated extension of NSCLC at thoracotomy in patients with borderline medical fitness for surgery.

Our finding that patients undergoing uncertain or incomplete resection were more likely to have received induction therapy (9.2% and 18.0%, respectively, versus 5.5% of patients undergoing complete resection; p=0.0001) is similar to those of previous reports [7,19]. Indeed, NSCLC patients with imaging findings suggestive of questionable surgical resectability are at higher likelihood of undergoing induction therapy and at higher risk for an incomplete resection.

As regards the types of surgery, it should be noted that sublobar resections, particularly wedge resections, were more frequently performed in patients with coexistent cardiopulmonary impairment and were associated with fewer or no dissected intrathoracic lymph nodes. Indeed, no lymph nodes were sampled in 23 (44.2%) of 52 patients undergoing wedge resection and in 2 (3.2%) of 62 patients undergoing segmentectomy. Patients who did not have lymph nodes sampled (pNx) had a 5-year survival rate similar to that of pN2 cohort, suggesting that a substantial proportion of pNx patients had missed lymph node metastasis. In addition, patients who had sublobar resection were significantly more likely to undergo an incomplete resection, as compared with patients who had major anatomic resection (14.0% and 6.3%, respectively; p=0.002). These observations are in accordance with the results of other large database studies and institutional series [18-20,23].

Perioperative outcomes were similar in the three study groups, but the uncertain and incomplete resection patients experienced a twofold higher rate of postoperative death. We hypothesize that this may be due to differences in comorbidity profile and administration of induction therapy.

Not unexpectedly, patients who underwent complete resection were more likely than those who underwent uncertain or incomplete resection to have a smaller tumor diameter and to have earlier staged tumors. In other words, surgical curability did decline with increasing tumor diameter and advancing disease stage [7,18,19].

In contrast with other authors [18,19], we found that compared with patients who did not have postoperative adjuvant therapy, OS was significantly worse for patients treated with adjuvant therapy. This observation likely reflects both a limited effectiveness of adjuvant therapy and an inherent selection bias whereby patients with more advanced disease stage were at higher likelihood of undergoing adjuvant therapy. Additionally, practice standards regarding referral of patients for adjuvant therapy and medical oncologic protocols were not uniformly established during the 10-year time frame of this study.

Several limitations regarding the present study should be considered. Retrospective single institution studies are inherently subject to unobserved confounding and selection bias. Further limitations arise from the long time interval of patient accrual, the small number of patients available for subgroup analyses, and lack of data concerning locoregional or distant recurrences and cause of death. However, follow-up was complete and all patients were followed up until death or for a minimum period of 5 years, with a median length for surviving patients at 109.6 months. Moreover, the prognostic significance of the IASLC definitions was verified by a multivariable analysis including well known patient-, disease-, and treatment-related prognostic factors.

In conclusion, the present analysis suggests that in patients undergoing surgery for NSCLC, the IASLC definitions of complete, uncertain and incomplete resection are associated with statistically significant differences in survival. Given the limitations of a retrospective analysis, further prospective study is needed to definitely confirm our findings.

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Conflict of Interest

All authors declare that there is no conflict of interest.

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Table

TABLE 1. Demographic and clinicopathologic data of the study population (n=1277)

Characteristic	Total n = 1277	Complete R n = 1003 (78.5%)	Uncertain R n = 185 (14.5%)	Incomplete R n = 89 (7.0%)	P Value
Age (years), median (IQR)	67 (61-72)	67 (61-71)	67 (61-73)	66 (61-72)	0.382
Gender					0.363
Male, n (%)	1024 (80.2)	812 (81.0)	145 (78.4)	67 (75.3)	
Female, n (%)	253 (19.8)	191 (19.0)	40 (21.6)	22 (24.7)	
Charlson Comorbidity Index					0.088
0, n (%)	566 (44.3)	457 (45.5)	68 (36.8)	41 (46.1)	
1-2, n (%)	616 (48.3)	479 (47.8)	99 (53.5)	38 (42.7)	
≥3, n (%)	95 (7.4)	67 (6.7)	18 (9.7)	10 (11.2)	
Induction therapy					0.0001
No, n (%)	1189 (93.1)	948 (94.5)	168 (90.8)	73 (82.0)	
Yes, n (%)	88 (6.9)	55 (5.5)	17 (9.2)	16 (18.0)	
Year of surgery					0.257
1998-2002, n (%)	570 (44.6)	436 (43.5)	92 (49.7)	42 (47.2)	
2003-2007, n (%)	707 (55.4)	567 (56.5)	93 (50.3)	47 (52.8)	
Surgery					0.0001
Pneumonectomy, n (%)	180 (14.1)	132 (13.2)	28 (15.1)	20 (22.5)	
Lobectomy, n (%)	983 (77.0)	818 (81.5)	112 (60.6)	53 (59.6)	
Segmentectomy, n (%)	62 (4.8)	40 (4.0)	17 (9.2)	5 (5.6)	
Wedge resection, n (%)	52 (4.1)	13 (1.3)	28 (15.1)	11 (12.3)	
Length of stay (days), median (IQR)	8 (7-11)	8 (7-11)	9 (7-11)	9 (7-12)	0.129
Postoperative morbidity*					
Any complication, n (%)	547 (42.8)	422 (42.1)	89 (48.1)	36 (40.4)	0.282
Major CP morbidity, n (%)	180 (14.1)	136 (13.6)	30 (16.2)	14 (15.7)	0.579
Operative mortality*					
30-day, n (%)	26 (2.0)	17 (1.7)	6 (3.2)	3 (3.4)	0.296
Perioperative, n (%)	34 (2.7)	22 (2.2)	8 (4.3)	4 (4.5)	0.171
90-day, n (%)	41 (3.2)	27 (2.7)	9 (4.9)	5 (5.6)	0.158
Histology					0.692
Adenocarcinoma, n (%)	706 (55.3)	553 (55.1)	103 (55.7)	50 (56.2)	
Squamous cell, n (%)	446 (34.9)	353 (35.2)	60 (32.4)	33 (37.1)	
Other, n (%)	125 (9.8)	97 (9.7)	22 (11.9)	6 (6.7)	

Tumor size (mm), median (IQR)	35 (25-50)	35 (25-45)	35 (25-45)	40 (30-60)	0.001
pT status					0.0001
T1, n (%)	297 (23.3)	250 (24.9)	39 (21.1)	8 (9.0)	
T2, n (%)	560 (43.8)	455 (45.4)	79 (42.7)	26 (29.2)	
T3, n (%)	304 (23.8)	230 (22.9)	40 (21.6)	34 (38.2)	
T4, n (%)	116 (9.1)	68 (6.8)	27 (14.6)	21 (23.6)	
pN status					0.0001
N0, n (%)	813 (63.7)	726 (72.4)	70 (37.8)	17 (19.1)	
N1, n (%)	220 (17.2)	191 (19.0)	12 (6.5)	17 (19.1)	
N2, n (%)	217 (17.0)	86 (8.6)	80 (43.3)	51 (57.3)	
Unknown, n (%)	27 (2.1)	0	23 (12.4)	4 (4.5)	
pTNM stage					0.0001
I, n (%)	496 (38.8)	447 (44.6)	48 (25.9)	1 (1.1)	
II, n (%)	379 (29.7)	348 (34.7)	22 (11.9)	9 (10.1)	
III-IV, n (%)	375 (29.4)	208 (20.7)	92 (49.7)	75 (84.3)	
Unknown, n (%)	27 (2.1)	0	23 (12.4)	4 (4.5)	
Adjuvant therapy					0.0001
No, n (%)	1023 (80.1)	884 (88.1)	109 (58.9)	30 (33.7)	
Yes, n (%)	254 (19.9)	119 (11.9)	76 (41.1)	59 (66.3)	

* As defined in the methods section.
R: resection; IQR: interquartile range; CP: cardiopulmonary

Table

TABLE 2. Survival of the study population (n=1277)

Variable	Crude HR	95%CI	P Value	Survival (months), median (95% CI)	5 year survival rate %
Age	1.028	1.020-1.037	0.0001		
Gender					
Female	1			90.6 (64.3-116.9)	59.3
Male	1.380	1.152-1.654	0.0001	61.8 (54.4-69.3)	51.1
Charlson Comorbidity Index					
0	1			85.5 (71.1-99.9)	57.5
1-2	1.435	1.244-1.655	0.0001	58.7 (47.8-69.6)	50.0
≥3	1.901	1.485-2.433	0.0001	48.9 (39.2-58.5)	40.0
Induction therapy					
No	1			69.3 (62.8-75.9)	53.6
Yes	1.102	0.840-1.446	0.484	28.7 (7.2-50.2)	40.9
Surgery					
Pneumonectomy	1			35.8 (20.3-51.3)	41.1
Lobectomy	0.788	0.653-0.951	0.013	72.8 (65.8-79.8)	55.7
Segmentectomy	0.801	0.562-1.143	0.221	76.4 (59.3-93.4)	58.1
Wedge resection	1.290	0.907-1.834	0.157	36.7 (21.5-51.9)	28.8
Completeness of resection					
Complete	1			80.1 (72.7-87.5)	58.8
Uncertain	1.690	1.412-2.024	0.0001	39.9 (33.3-46.6)	37.3
Incomplete	3.177	2.514-4.016	0.0001	17.3 (13.9-20.7)	15.7
Major CP postop morbidity*					
No	1			70.4 (63.2-77.6)	54.1
Yes	1.266	1.050-1.528	0.014	46.8 (33.5-60.1)	44.4
Histology					
Adenocarcinoma	1			70.1 (62.4-77.9)	53.4
Squamous	0.982	0.849-1.136	0.806	64.1 (49.4-78.8)	52.2
Other	1.028	0.813-1.299	0.821	63.0 (39.3-86.7)	50.4
Tumor size (mm)	1.010	1.006-1.013	0.0001		

pT status					
T1	1			110.6 (93.4-127.8)	69.7
T2	1.494	1.239-1.801	0.0001	69.3 (59.5-79.2)	54.6
T3	2.060	1.679-2.528	0.0001	33.9 (25.1-42.6)	37.5
T4	2.333	1.805-3.015	0.0001	36.7 (19.3-54.1)	39.7
pN status					
N0	1			86.6 (77.7-95.4)	62.2
N1	1.563	1.307-1.869	0.0001	37.4 (21.9-52.9)	43.6
N2	2.281	1.922-2.708	0.0001	27.6 (20.6-34.6)	29.0
Unknown	2.096	1.379-3.187	0.001	38.9 (10.5-67.4)	29.6
pTNM stage					
I	1			99.7 (87.2-112.1)	68.8
II	1.355	1.140-1.610	0.001	71.6 (56.5-86.6)	53.6
III-IV	2.493	2.116-2.938	0.0001	27.6 (21.9-33.3)	32.3
Unknown	2.428	1.585-3.720	0.0001	38.9 (10.5-67.4)	29.6
Adjuvant therapy					
No	1			78.9 (71.0-86.9)	57.9
Yes	1.889	1.616-2.208	0.0001	29.7 (22.4-37.0)	31.9

* As defined in the methods section.

HR: hazard ratio; CI: confidence interval; CP: cardiopulmonary

Table

TABLE 3. Cox proportional hazard model of survival of the study population (n=1277)

Variable	Adjusted HR	95%CI	P Value
Age	1.025	1.016-1.034	0.0001
Gender			
Female	1		
Male	1.286	1.068-1.549	0.008
Charlson Comorbidity Index			
0	1		
1-2	1.300	1.122-1.507	0.0001
≥3	1.530	1.187-1.972	0.001
Completeness of resection			
Complete	1		
Uncertain	1.352	1.101-1.661	0.004
Incomplete	2.299	1.787-2.957	0.0001
pT status			
T1	1		
T2	1.350	1.119-1.631	0.002
T3	1.854	1.507-2.280	0.0001
T4	1.878	1.446-2.439	0.0001
pN status			
N0	1		
N1	1.437	1.201-1.721	0.0001
N2	1.840	1.520-2.228	0.0001
Unknown	1.173	0.742-1.854	0.494

HR: hazard ratio; CI: confidence interval