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ORIGINAL ARTICLE

Chest wall/parietal pleural invasions worsen prognosis in T4 non-small cell lung cancer patients after resection

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Abstract

Objectives Appropriate selection for surgery is particularly important in T4 non-small cell lung cancer patients. In clinical settings, patients those who are positive for T4 criteria occasionally are also positive for T3 factors which are independently defined from original T4 or even have multiple T4 factors. Significance of these factors on prognosis is still unknown.

Methods We retrospectively reviewed clinicopathorogical data of 113 patients with T4 non-small cell lung cancer those who underwent surgery between 1990 and 2015 in Tohoku University Hospital. Significance on prognosis of single or multiple T4 factors and with or without independent T3 factors were statistically analyzed.

Results No significant difference was seen in the 5-year survival rate between patients with single (35.6%) and multiple (31.4%) T4 factors ($P=0.94$), but the rate was significantly lower when patients also had independent T3 factors (19.6%) compared with when they did not (42.5%) ($P=0.011$). The 5-year survival rate was particularly lower among patients with invasion of the chest wall or parietal pleura (8.1%) than in those without (40.6%) ($P=0.0052$).

Conclusions Invasion of the chest wall or parietal pleura is poor prognostic factors in T4 non-small cell lung cancer patients.

Keywords T4 lung cancer · Prognostic factor · Surgical resection · 5-Year survival rate

Introduction

T4 non-small cell lung cancer (NSCLC) is a locally advanced disease with a poor prognosis. Recent studies have reported the 5-year survival rate after surgery to be 19.1–38.4% [1–6], whereas overall morbidity and mortality are reported to be 35–52% and 4–19.1%, respectively [2, 3, 6, 7]. Therefore, although surgery for T4 disease is challenging, it is worthwhile and can effectively cure substantial numbers of patients. T4 NSCLCs are a heterogeneous group of locally advanced disease [6]. Knowing the prognostic factors is critical to assessing surgical candidates. Current evidence indicates that microscopic residue (R1) or macroscopic residue (R2) of tumor cells, pathological nodal (pN) status (specifically, pN2), pneumonectomy, and pericardial invasion are the poor prognostic factors [2, 3, 8, 9]. In clinical practice, it is also true that some patients have multiple T4 factors or have T3 factors in addition to T4 factors. Especially, chest wall or parietal pleural invasion is sometimes existed in T4 NSCLC patients. However, it is unknown whether these patient groups have the same prognosis as those who have a single T4 factor. In this study, we retrospectively investigated how these combinations of factors affected outcomes after surgical resection in patients with T4 NSCLC.

Subjects

We retrospectively included patients who underwent surgical resection for T4 NSCLC at Tohoku University Hospital between 1990 and 2015. All included patients were re-staged using the latest tumor, nodal, and metastasis (TNM) classification [10]. All data were obtained from medical records.

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The study was approved by the institutional review board of our hospital (2018-1-124-1).

Methods

The 5-year survival rate was examined and compared based on whether single or multiple T4 factors were present, and the presence or absence of 'independent T3 factors' in the presence of T4 factors. Univariate analysis was performed on each independent T3 factor for detecting prognostic factors in independent T3 factors, and the 5-year survival rate was examined and compared based on the significant factors on the univariate analysis. To determine the prognostic factors, univariate analysis was performed on the following factors: age, sex, surgical procedures, tumor histological type, smoking history, induction therapy, adjuvant therapy, pathological N status, whether single or multiple T4 factors were present, and the presence or absence of independent T3 factors in the presence of T4 factors. Using significant factors in univariate analysis, multivariate analysis was performed.

T3 factors accompanied by T4 factors were not considered an "independent T3 factor". For example, the invasion of vertebral body inevitably has the invasion of the parietal pleura; however, the invasion of vertebral body was considered as a single T4 factor without independent T3 factor. Also, T4 factor of tumor size > 70 mm implements tumor size > 50 mm, which includes in T3 factor, but tumor size > 70 mm was considered as a single T4 factor without independent T3 factor. Instead, T3 factors that were not accompanied by T4 factors were considered as independent T3 factors. For example, in a case, where an 80-mm tumor invaded the chest wall, it was considered as T4 NSCLC with an independent T3 factor. Also, when a tumor invaded into the diaphragm and the parietal pleura, it was considered as T4 NSCLC with an independent T3 factor.

The survival rates were represented by overall 5-year survival rates. Postoperative death included all-cause deaths within 30 days of surgery and before discharge from hospital.

Statistical analysis

The continuous variables were represented as average ± standard error. The follow-up period was also represented by median (first quartile–third quartile). The 5-year overall survival rate was calculated by the Kaplan–Meier method and statistically compared by the log-rank test. When the follow-up period did not reach 5 years, the case was dealt as a censoring. The Fisher exact test was used to compare nominal variables, and Cox proportional hazards regression analysis was used for univariate and multivariate analysis. Statistical significance was set at $P < 0.05$, and the EZR software (Ver. 1.32, Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for statistical analysis [11].

Results

We included 113 patients (average age of 63.3 ± 11.0 years), of which 94 were male. The average follow-up period was 42.1 ± 5.0 months, and the median was 20.7 (8.1–55.1) months. The characteristics of all patients are shown in Table 1. The most common T4 factor was tumor size > 70 mm, and the overall 5-year survival rate was 35.0%. The numbers of patients treated by induction therapy and adjuvant therapy were 17 and 20, respectively. Overall, 4 patients died within 30 days after surgery, giving a postoperative mortality of 3.5%. The cause of death was pneumonia for 2 patients, brain infarction for 1 patient, and failure of a tracheal suture for 1 patient. Four patients did not undergo mediastinal nodal dissections, and the diameters of tumor were not measured in 2 patients.

Table 1 Characteristics of all patients

Factor	Number of patients
Age (< 70 years/≥ 70 years)	83/36
Sex (male/female)	94/19
Smoking (< 30-pack-year/≥ 30-pack-year)	36/66
Histological type (Ad/Sq/LCNEC/others)	36/52/13/12
T4 factor	
Tumor size > 70 mm	63
Visceral pericardium invasion	17
Great vessel invasion	16
Diaphragm invasion	10
Ipsilateral metastasis in non-primary lobe	10
Trachea or carina invasion	7
Mediastinum invasion	6
Esophagus invasion	3
Vertebral invasion	2
Brachial plexus invasion	2
Tumor size (≤ 50 mm/50–70 mm/> 70 mm)	34/14/63
Induction therapy (±)	17/96
Adjuvant therapy (±)	20/93
Surgical procedure	
Pneumonectomy/lobectomy/sub-lobar resection	40/71/2
Pathological nodal status (N0/N1/N2)	44/23/42
Completeness of resection (R0/R1/R2)	89/5/19

Ad adenocarcinoma, *Sq* squamous cell carcinoma, *LCNEC* large cell neuroendocrine carcinoma

Analysis on multiple T4 factors and independent T3 factors

In the present study, we identified 20 patients (17.7%) with multiple T4 factors, among whom the most common combination was tumor size > 70 mm with visceral pericardial invasion, as shown in Table 2. The 5-year survival rates were not significantly different between patients with multiple (31.4%) and single (35.6%) T4 factors ($P = 0.94$; Fig. 1). The ratios for those undergoing R0 resection or having pN2 status were comparable between patients with single (77.8% and 36.7%, respectively) and those with multiple (65.0% and 45.0%, respectively) T4 factors ($P = 0.12$ and $P = 0.44$, respectively). Also, we identified that 34 patients (30.1%) had independent T3 factors in addition to at least one T4 factor, with the most common T3 factors being invasion of the chest wall or parietal pleura (19 patients; 16.8%) (Table 2). The 5-year survival rates were significantly lower in patients with independent T3 factors (19.6%) than in those without independent T3 factors (42.5%; $P = 0.011$; Fig. 2). The ratios for those undergoing R0 resection or having pN2 status were comparable between patients with independent T3 factors (77.2% and 45.5%, respectively) and those without (83.1% and 35.5%, respectively) ($P = 0.21$ and $P = 0.39$, respectively).

Table 2 Number of patients with multiple T4 factors by combination and independent T3 factors

Multiple T4 factors/independent T3 factors	Number of patients
Multiple T4 factors	20
Tumor size > 70 mm	
+ Visceral pericardium invasion	5
+ Diaphragm invasion	3
+ Ipsilateral metastasis in non-primary lobe	2
+ Esophagus invasion	1
+ Great vessel invasion	1
+ Mediastinum invasion	1
+ Vertebral and diaphragm invasion	1
+ Visceral pericardium and diaphragm invasion	1
Great vessel invasion	
+ Visceral pericardium invasion	3
+ Trachea/carina invasion	1
+ Esophagus invasion	1
Independent T3 factors	34
Chest wall/parietal pleura invasion	19
Tumor size: 51–70 mm	14
Pulmonary metastasis in primary lobe	6
Mediastinal pleura invasion	3

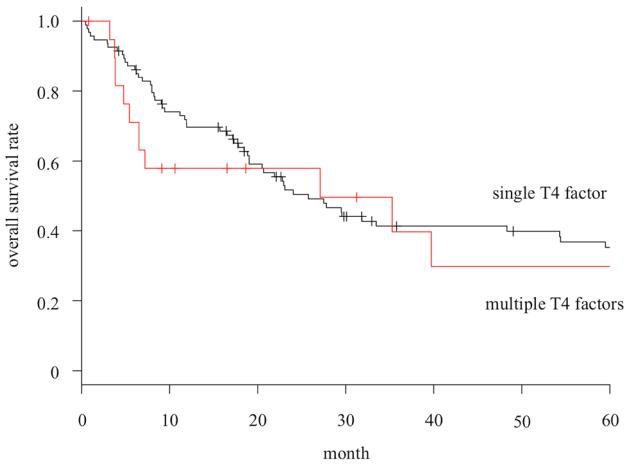

Fig. 1 Kaplan–Meier curves for patients with single or multiple T4 factors. There was no significant difference in the 5-year survival rate for single T4 factor ($n = 94$; 35.6%) and multiple ($n = 19$; 31.4%) T4 factors

Multivariate analysis on independent T3 factors

The result of multivariate analysis on each independent T3 factor is shown in Table 3. Only chest wall or parietal pleural invasion was significant among these 4 independent T3 factors, giving the significant difference in 5-year survival rates between patients with invasions of the chest wall or parietal pleura and patients without them (8.1% and 40.6%, respectively; $P = 0.0052$; Fig. 3). Notably, the ratios for those undergoing R0 resection or having pN2 status were

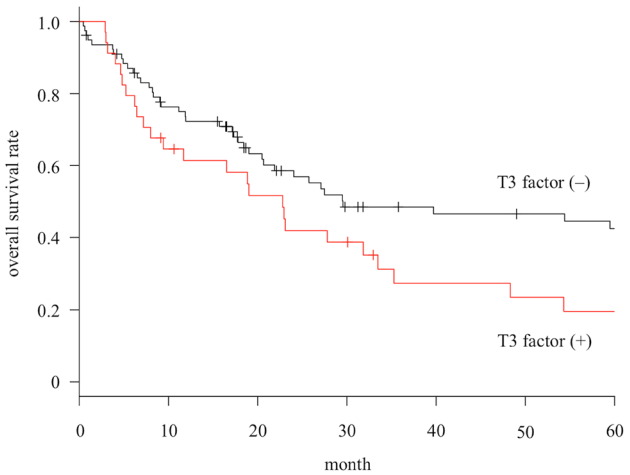

Fig. 2 Kaplan–Meier curves for T4 NSCLC patients with and without independent T3 factors. In patients with T4 factors, the 5-year survival rate when independent T3 factors were present ($n = 34$; 19.6%) was significantly lower than that when independent T3 factors were absent ($n = 79$; 42.5%, $P = 0.011$). T3 factor (+): T4 NSCLS patients with independent T3 factors. T3 factor (−): T4 NSCLC patients without independent T3 factors

Table 3 Multivariate analysis on survival among independent T3 factors

Factor	HR	95% CI	*P* value
Tumor size (51–70 mm)	0.89	0.45–1.75	0.73
Visceral pleural invasion	1.05	0.30–3.72	0.94
Metastasis in primary lobe	1.01	0.35–2.88	0.99
Chest wall/parietal pleural invasion	2.13	1.14–3.72	0.018

HR hazard ratio, *CI* confidence interval

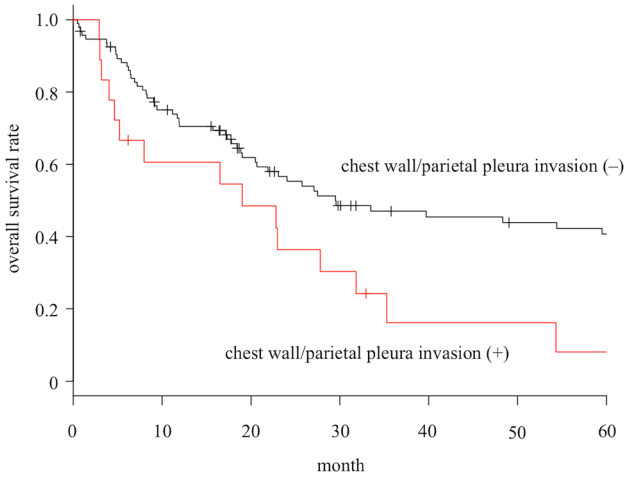

Fig. 3 Kaplan–Meier curves for T4 NSCLC patients with and without invasion of the chest wall or parietal pleura. In patients with T4 factors, the 5-year survival rate when patients had invasion of the chest wall or parietal pleura ($n=19$; 8.1%) was significantly lower than that when patients did not have invasion of the chest wall or parietal pleura ($n=94$; 40.6%, $P=0.0052$). Chest wall/parietal pleura invasion (+): T4 NSCLC patients with invasion of the chest wall or parietal pleura. Chest wall/parietal pleura invasion (−): T4 NSCLC patients without invasion of the chest wall or parietal pleura

not significantly different between patients with (68.4% and 50.0%, respectively) and without (81.9% and 63.7%, respectively) invasion of the chest wall or parietal pleura ($P=0.21$ and $P=0.30$, respectively). In addition, the average tumor sizes in patients with and without invasion of the chest wall or parietal pleura were 72.1 ± 37.4 mm and 68.8 ± 29.4 mm, respectively ($P=0.68$).

Univariate and multivariate analysis for detecting prognostic factors on survival

As shown in Table 4, female sex, smoking history more than 30-pack-year, chest wall or parietal pleural invasion, pathological N2, and R1/R2 resection were significant prognostic factors on survival in the univariate analysis. In the multivariate analysis, pathological N2 and R1/R2 resection were significant.

Discussion

We showed that the presence of independent T3 factors was associated with a poor prognosis after surgical resection in patients with T4 NSCLC. Of these, the invasion of the chest wall or parietal pleura was associated with particularly poor survival outcomes.

In the present study, the 5-year survival rate was significantly lower in patients with independent T3 factors, especially those with chest wall/parietal pleural invasion although the significant difference was not observed between patients with single T4 factor and those with multiple T4 factors. Notably, the ratios of patients who underwent R0 resection and have pN2 were not significantly different between each comparison. There are two possible reasons to

Table 4 Univariate and multivariate analyses on survival

Univariate analysis				Multivariate analysis		
Factor	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥ 70 years	1.18	0.71–1.96	0.53			
Female	0.44	0.20–0.95	0.037	0.50	0.19–1.29	0.15
Pneumonectomy	1.16	0.70–1.91	0.56			
Adenocarcinoma	0.87	0.52–1.43	0.57			
Smoking ≥ 30-pack-year	1.91	1.11–3.30	0.019	1.52	0.78–2.94	0.22
Induction therapy	0.92	0.49–1.72	0.80			
Adjuvant therapy	0.84	0.51–1.36	0.470			
Multiple T4 factors	1.03	0.52–2.01	0.94			
Chest wall/parietal pleural invasion	2.11	1.21–3.68	0.0083	1.85	0.98–3.49	0.059
Pathological N2	2.08	1.28–3.39	0.0031	2.12	1.20–3.77	0.010
R1/2 resection	2.97	1.75–5.06	< 0.001	2.01	1.03–3.92	0.040

HR hazard ratio, *CI* confidence interval

explain the effect of independent chest wall/parietal pleural invasion on the prognosis after the resection of T4 NSCLC patients. First, the differences in lymph vessels and capillaries may affect the prognosis when the tumor invades the parietal pleura. T4 factors other than tumor size > 70 mm and metastasis in the non-primary lobe obviously indicate invasion into mediastinal organs, and these can invade lymph vessels and capillaries in the mediastinal pleura. Conversely, T4 NSCLC with independent invasion of the chest wall or parietal pleura can invade lymph vessels and capillaries not only in mediastinal pleura but also in parietal pleura, which may worsen the survival after resection. The survival rate of patients with multiple T4 factors was comparable to that of patients with a single T4 factor in the present study, which may support this hypothesis. Second is the resulting of surgical stress. The resection of chest wall or parietal pleura could imply additional stress on patients. A high degree of surgical stress could affect long-term survival.

The TNM classification is an established staging system, but it continues to be updated periodically by the International Association for the Study of Lung Cancer International Staging Project [10]. Although only the most advanced T factor is adopted in the staging system, even when two or more are present, it might be difficult to combine multiple T factors, because it would make the staging system complicated. Despite this, it is undoubtable that combining multiple T factors may be useful in determining the appropriateness of surgery in patients at high risk of poor morbidity and mortality rates, such as patients with T4 NSCLC.

According to previous studies [2–5, 8, 9, 12–14], both R0 resection and the presence of confirmed pN0/N1 status were significantly associated with a good prognosis in patients with T4 NSCLC. Previous studies have indicated that the 5-year survival rates for R0 and R1/R2 resections in these patients were 40.4–58.3% and 10.9–15.9%, respectively [2, 7]. Also, the 5-year survival rates in T4 NSCLC patients and either pN0/N1 or pN2 status were 37.5–44.9% and 0–17.5%, respectively [2, 15]. Although chest wall/parietal pleural invasion could not reach the significance in the multivariate analysis in the present study ($P = 0.059$), chest wall/parietal pleural invasion may be an independent prognostic factor in T4 NSCLC patients, considering the small number of patients (19 patients) and the comparable ratios of patients who underwent R0 resection and have pN2 in the comparison. General preoperative decision according to probability of R0 resection, exclusion of pN2, and total surgical stress should be made. Although preoperative prospect for R0 resection for T4 disease is sometimes difficult, evaluation of T3 disease including chest wall invasion is relatively easy by computed tomography. Furthermore, according to the recent meta-analysis, the negative predictive value for pN2 by endobronchial ultrasound-guided transbronchial needle aspiration has been reported to be about 90% [16], suggesting that the preoperative prediction of pN2 was difficult.

In the present study, the number of patients treated by induction therapy was small, because the effect of induction therapy on long-term survival was unclear and controversial in patients with T4 NSCLC [17–19]. Yildizeli et al. [2] reported that the 5-year survival rates in patients with T4 NSCLC were 37.0% with induction therapy and 38.8% without induction therapy, concluding that it did not improve outcomes. Other researchers have also showed that induction therapy was associated with increased morbidity after surgical resection [20]. In research conducted by Matsubara et al. [21], the morbidity and mortality rates after extended surgery with induction therapy were 55.4% and 5.4%, respectively; the corresponding rates in the initial surgery group were 16.8% and 0%. Given that induction therapy decreases the size of the primary tumor to achieve complete resection, it might remain a viable option in appropriately selected patients with T4 NSCLC [18].

The present study has several limitations. First, this is a retrospective study with the inherent biases of such a design. For example, patients with T4 NSCLC who underwent surgical resection were specially selected based on preoperative morbidity and performance status. Second, the present data were collected over a 25-year period, during which time chemotherapy regimens have changed and improved. The role of chemotherapy in this study is probably limited by this, indicating that any associated data should be interpreted with care. However, there is no patient who underwent therapies with epidermal growth factor receptor tyrosine kinase inhibitor or immune checkpoint inhibitor. Finally, the number of patients who received adjuvant chemotherapy was small in this study because of their poor performance status or general conditions after the surgical resection.

Conclusion

In conclusion, the presence of independent T3 factors, specifically invasion of chest wall or parietal pleura invasion, may predict poor survival. This should be carefully considered when evaluating the suitability of patients as surgical candidates in T4 NSCLC.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Watanabe S, Asamura H, Miyaoka E, Okumura M, Yoshino I, Fujii Y, et al. Results of T4 surgical cases in the Japanese Lung Cancer Registry Study: should mediastinal fat tissue

invasion really be included in the T4 category? J Thorac Oncol. 2013;8(6):759–65.
2. Yildizeli B, Dartevelle PG, Fadel E, Mussot S, Chapelier A. Results of primary surgery with T4 non-small cell lung cancer during a 25-year period in a single center: the benefit is worth the risk. Ann Thorac Surg. 2008;86(4):1065–75 **(discussion 74–5)**.
3. Stella F, Dell'Amore A, Caroli G, Dolci G, Cassanelli N, Luciano G, et al. Surgical results and long-term follow-up of T(4)-non-small cell lung cancer invading the left atrium or the intrapericardial base of the pulmonary veins. Interact Cardiovasc Thorac Surg. 2012;14(4):415–9.
4. Wu L, Xu Z, Zhao X, Li J, Zhong L, Pang T, et al. Surgical treatment of lung cancer invading the left atrium or base of the pulmonary vein. World J Surg. 2009;33(3):492–6.
5. Osaki T, Sugio K, Hanagiri T, Takenoyama M, Yamashita T, Sugaya M, et al. Survival and prognostic factors of surgically resected T4 non-small cell lung cancer. Ann Thorac Surg. 2003;75(6):1745–51 **(discussion 51)**.
6. Rice TW, Blackstone EH. Radical resections for T4 lung cancer. Surg Clin North Am. 2002;82(3):573–87.
7. Pitz CC, Brutel de la Riviere A, van Swieten HA, Westermann CJ, Lammers JW, van den Bosch JM. Results of surgical treatment of T4 non-small cell lung cancer. Eur J Cardiothorac Surg. 2003;24(6):1013–8.
8. Riquet M, Grand B, Arame A, Pricopi CF, Foucault C, Dujon A, et al. Lung cancer invading the pericardium: quantum of lymph nodes. Ann Thorac Surg. 2010;90(6):1773–7.
9. Yang HX, Hou X, Lin P, Rong TH, Yang H, Fu JH. Survival and risk factors of surgically treated mediastinal invasion T4 non-small cell lung cancer. Ann Thorac Surg. 2009;88(2):372–8.
10. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39–51.
11. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transpl. 2013;48(3):452–8.
12. Ohta M, Hirabayasi H, Shiono H, Minami M, Maeda H, Takano H, et al. Surgical resection for lung cancer with infiltration of the thoracic aorta. J Thorac Cardiovasc Surg. 2005;129(4):804–8.
13. Chambers A, Routledge T, Bille A, Scarci M. Does surgery have a role in T4N0 and T4N1 lung cancer? Interact Cardiovasc Thorac Surg. 2010;11(4):473–9.
14. Dartevelle PG, Mitilian D, Fadel E. Extended surgery for T4 lung cancer: a 30 years' experience. Gen Thorac Cardiovasc Surg. 2017;65(6):321–8.
15. Misthos P, Papagiannakis G, Kokotsakis J, Lazopoulos G, Skouteli E, Lioulias A. Surgical management of lung cancer invading the aorta or the superior vena cava. Lung Cancer. 2007;56(2):223–7.
16. Leong TL, Loveland PM, Gorelik A, Irving L, Steinfort DP. Preoperative staging by EBUS in cN0/N1 lung cancer: systematic review and meta-analysis. J Bronchol Interv Pulmonol 2018. https://doi.org/10.1097/LBR.0000000000000545
17. DiPerna CA, Wood DE. Surgical management of T3 and T4 lung cancer. Clin Cancer Res. 2005;11(13 Pt 2):5038s-44 s.
18. Lococo F, Cesario A, Margaritora S, Dall'Armi V, Nachira D, Cusumano G, et al. Induction therapy followed by surgery for T3-T4/N0 non-small cell lung cancer: long-term results. Ann Thorac Surg. 2012;93(5):1633–40.
19. Grunenwald DH, Andre F, Le Pechoux C, Girard P, Lamer C, Laplanche A, et al. Benefit of surgery after chemoradiotherapy in stage IIIB (T4 and/or N3) non-small cell lung cancer. J Thorac Cardiovasc Surg. 2001;122(4):796–802.
20. Roberts JR, Eustis C, Devore R, Carbone D, Choy H, Johnson D. Induction chemotherapy increases perioperative complications in patients undergoing resection for non-small cell lung cancer. Ann Thorac Surg. 2001;72(3):885–8.
21. Matsubara Y, Takeda S, Mashimo T. Risk stratification for lung cancer surgery: impact of induction therapy and extended resection. Chest. 2005;128(5):3519–25.