Int J Clin Exp Med 2015;8(7):11675-11682
www.ijcem.com /ISSN:1940-5901/IJCEM0009145

Review Article

Controversies regarding T status and N status for non-small cell lung cancer

Yanli Mo[1], Jiayin Peng[2], Wenmei Su[1], Xinggui Chen[1], Aibing Wu[1], Jinmei Li[1], Zhixiong Yang[1]

[1]Department of Oncology, Affiliated Hospital of Guangdong Medical University, 57 Renmin Road, Zhanjiang, PR China; [2]Department of Urology, Zhanjiang Central People's Hospital, 2 Cunjin Road, Zhanjiang, PR China

Received April 15, 2015; Accepted June 10, 2015; Epub July 15, 2015; Published July 30, 2015

Abstract: According to the newest version of NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer (NSCLC), increasing attentions are paid to the role of nodal status and other high-risk factors, including vascular invasion, wedge resection, tumors > 4 cm, visceral pleural involvement, and incomplete lymph node sampling in the individual clinical treatment. Precise definitions of T status and N status, closely associated with prognosis and treatment, are worth expanding further. However, complexity arises because no unity definition exists regarding individual T and N descriptors. In an attempt to explore the potential prognostic values of the T status and N status, we systematically review relevant literature and found that there still remained some disputes about the definitions and prognosis. The adjacent lobe invasion regarded as T2 or T3 has not been reached consensus yet so far. Lymph node spread patterns are associated with the treatment strategies of NSCLC. This review mainly focus on the role of T status and N status and tried to seek appropriate and individual treatment strategies in NSCLC.

Keywords: Non-small cell lung cancer, t status, n status, lymph node, prognosis

Introduction

Lung cancer is still the leading cause of cancer mortality in the world and has a poor survival prognosis in spite of the great improvement for comprehensive treatments [1]. Therefore, further research is needed. Nowadays, clinical staging and pathological staging remain the dominating staging classification. Accurate staging is increasing thought to be the most important prognostic factor and to confirm the most adequate treatment strategy in NSCLC [2]. For example, precise definitions of T status and N status, which survival rates still remain disputed, are expected to expand even further. Current researches have made many comparisons of survival in patients with NSCLC according to specific definitions of T status and N status, completeness of resection, location and size of tumor, primary T status, numbers of positive lymph node stations and post-operative adjuvant therapy. But they haven't reached a consensus yet, due to no unity definition regarding individual T and N descriptors. The followings retrospect details about the various factors likely to affect the survival rates and prognosis of specific T status and N status in studies and discuss areas in which ambiguities and differences exist.

T status

pT factor affects TNM staging?

The impact of T factor seems to remain controversial. In most previous studies, pT stage is closely associated with prognosis of lung cancer. The earlier the T stage, the better the prognosis [3, 4]. The 5-year survival rates of patients with T1, T2, and T3 disease are ranging 31.5%-62%, 24.3%-53%, and 43%-49%%, respectively [4-8]. Patients with T4 tumors has a 3-year survival rate of 45% and a 5-year survival rate of 11.1% [5, 7]. The result of study by Haam SJ et al. [8] indicates patients with the T2 groups have better survival prognoses than the T3 groups ($P < 0.0001$). However, some address that T factor may have nothing to do with the survival [9, 10]. Detterbeck FC et al. [11] reports there is no statistical difference from the patients (T1b vs T2a, $P = 0.85$; T2a vs T2b, $P =$

0.71; T2b vs T2c, $P = 0.81$; T2c versus T3, $P = 0.47$). Demir A et al. [7] also note that there is no significant stratification in survival rates among patients with T1 and T2 ($P = 0.1$), T2 and T3 ($P = 0.18$), or T3 and T4 disease ($P = 0.63$) which is consistent with the above results. Based on the above results, we can better understand the latest 7th edition of the TNM staging system, which reveals that only patients with T1a and T2b tumors had prominently different survival times for lung cancer. As well as, it shows that pT factor doesn't play a major role in the survival rate except in case of the T4 disease regarded as stage III [12]. Similarly, there is no significant difference in the postoperative survival between patients with pT1N1M0 and those with pT2N1M0 [13-15]. The noteworthy heterogeneity of N1 disease with single-station N1, multiple-station, or comparatively small number of patients in T1 tumors may be well reasonably interpreted this result. As to the dissatisfied accessory examination, reports vary about the true rate of occult T1N2 patients. Defranchi SA et al. [6] observe that true pT1 NSCLC has a lower incident of N2 disease, especially for the rate of occult N2 disease, suggesting that routine invasive staging by mediastinoscopy should be avoided for patients with clinical T1 and negative noninvasive mediastinal staging [16, 17].

The adjacent lobe invasion, regarded as T2 or T3?

Dispute arises in the classification of the adjacent lobe invasion or interlobar pleural invasion. It is ambiguous as to which invading the adjacent lobe invasion should be classified as T2 or T3. Some recommend the adjacent lobe invasion should be classified as T2 when comparing the overall survival between patients with the adjacent lobe invasion and T3, which exhibited no statistically different survival rate from them [18, 19]. Ohtaki Y et al. [20] even categorize the adjacent lobe invasion into two types, one is beyond the incomplete fissure (ALI-D) and other is across the complete interlobar fissure (ALI-A). By comparing the survival of two groups, they find the interlobar fissure status has effect on the survival of patients with the adjacent lobe invasion. There exits significantly survival differences between the patients with ALI-A and ALI-D ($P = 0.010$). The survival of patients with ALI-A is similar to that of patients with T2b ($P = 0.846$) whereas the survival of patients with ALI-D has no distinct difference from those with T1a or T1b tumors ($P = 0.765$ and 0.418, respectively). According to this result, they make a conclusion that the ALI-A with a size of ≤ 5 cm should be regarded as T2b. However, the above result is lacking powerful persuasion because the number of cases is so finite. On the contrary, some fight against that it is appropriate to regard the adjacent lobe invasion as T3 rather than T2 [8, 21, 22]. Demir A et al. [22] report there is no remarkable difference between the overall survival of the patients with adjacent lobe invasion and those with T3 disease ($P = 0.67$). Four years later, Haam SJ et al. [8] also find a similar discovery to the above study. The overall survival of the patients with adjacent lobe invasion is not notable different from those with T3 disease ($P = 0.368$), but is distinct poorer than that of T2 patients ($P = 0.042$). During surgery, on account of the difficulty of identification for the border with adjacent lymph node stations, lymph nodes resection is not considered separate stations only [23]. With respect to classification and the optimal treatment of the adjacent lobe invasion, it hasn't been reached consensus yet so far. As accurate staging is regarded as the merit of a lymph node resection, we need to do a great effort, such as a meta-analysis or a multiple-center retrospective study, to make it clearer.

What about prognosis of the T4 NSCLC?

The T4 disease is regarded as tumor of any size with invasion of: heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina. Refer to the T4 disease, some report hopeful survival rates are ranging between 30% and 40% in the T4 patients with no mediastinal lymph node metastases and complete resection [24, 25]. The aortic resection-reconstruction for single station node positive T4 disease is related to better survival prognoses than sub-adventitial dissection while resection of the T4N2 NSCLC with disappointing survival rate is not promoted [9, 26]. Wex P et al. [9], who review 13 patients with N1 unsuspected N2 T4 NSCLC and aortic involvement, reveal that patients after aortic resection have a 5-year survival rate of 67% with a median survival time of 35 months. The survival rates don't statistically differ between N1 and

N2 nodal status (N1 vs N2/3; 52% vs 39% at 5 years; P = 0.998) for patients with T4 NSCLC. This observation shows that the T4 disease, unlike the T1, T2, T3 disease, plays a certain role in the survival rate as a particular characteristic of lung cancer, which is consistent with those of previous reports.

N status

Lymph node spread patterns

Previous to the specific N status, we discuss the characteristics of lymph node spread patterns, because which are closely associated with the treatment strategies of NSCLC. Latest researches show patterns of mediastinal lymph node metastases are related to the location of the primary tumor. As a whole, upper-lobe tumors are prone to metastasis to the upper region, lower-lobe tumors mainly metastasize to the lower region [10, 14, 27-29]. Recent reports have published that right upper lobe (RUL) tumors are more likely to have right upper (RU) mediastinal lymph node metastases, but rarely in the subcarinal (SC) zone. And those from left upper lobe (LUL) tumors are seemed to have most frequently in the AP or left upper (LU) region, whereas those lower lobe tumors rarely appear in the upper mediastinal region [14, 27]. Moreover, patients with left lower lobe (LLL) mostly have non-regional mode of spread [14, 27]. For the patients with the single-zone metastasis group, both lower lobe tumors mostly tend to involve the SC zone [10, 28]. What's more, upper-lobe tumors are mostly prone to metastasis to the hilar lymph nodes (no. 10), and lower-lobe tumors have most frequency in the interlobar lymph nodes (no. 11) [29]. What about the differences of lymph node metastasis on both sides tumors? On the right side, pN0 mostly occurred in the case of RUL, pN1 is more likely in the case of right lower lobe (RLL), whereas, pN2 has no difference in the frequency among all lobes. The difference in the frequency is not significant when considering the left side [14]. Patients with right middle lobe (RML) cancer most commonly have N1 disease [26] and more easily metastasize to more than two mediastinal lymph node stations [30]. It is controversial as to regard the differences on both sides of tumors with involvement of N2 disease. The right side tumors are more likely to have N2 disease than the left side tumors (27% vs 21%, P = 0.02) [26]. However, Riquet M et al. [14] delivers the right side tumors have similar frequency of single-station N2 involvement to the left side tumors (95% vs 94%). Considering to the two-nodal zones, right sided tumors commonly metastasize to the upper and SC region, meanwhile left upper lobe (LUL) tumors mainly to the upper and AP region. In addition, lower lobe tumors chiefly metastasize to SC and lower region. The unsuspected N2 patients have two-thirds single nodal zone metastasis, one-third multiple nodal zone metastasis. Meanwhile, the single-zone unsuspected N2 patients are similar to multiple-zone unsuspected N2 patients in the overall survival rate and disease-free survival rate [13]. The best explanation for the above outcome divergences was that the differences in staging for the N status was large and undefined. From the above, Cerfolio RJ et al. [26] make a proposal that LUL tumors could be thought about video-assisted thoracoscopy for biopsy of the 5 and 6 stations, RUL tumors could go through mediastinoscopy, while the RLL, LLL, and RML tumors might have esophageal ultrasound with fine-needle aspiration. Shimada Y et al. [27] suggest the lower lobe tumors, which have no metastasis to hilar, subcarinal, and lower mediastinal nodes on frozen sections, are unnecessary to have upper mediastinal lymph nodes dissection. Besides, the upper lung tumors with no metastasis to hilar and upper mediastinal lymph nodes were not necessary to have subcarinal dissection. Comparing with the upper lobe tumors, the lower lobe tumors have significantly poorer disease-free 5-year survival rate (27.9 % vs 11.1%, P = 0.007) [31]. Patients with SC metastasis had poorer overall survival rate, which were on account of more multiple-zone metastasis possibly [28]. Cerfolio RJ et al. [26] discover the LUL tumors often have skip metastases (no N1, but N2 disease), but Misthos P et al. [30] find skip metastases are more frequently in the right upper lobe tumors. Reason for this variance is that they are not randomized, lack rigorous, or involve remarkable in homogeneity in the study.

Prognosis of subdivided N1 NSCLC

The location of the primary tumors has a lot to do with the presence of lymph node metastases (pN). The 5-year disease free survival rates of patients with pN0, pN1, and pN2 disease are

showed 60.4%, 44.1%, 29.4% respectively, which indicate a favorable survival in the pN0 group compared with that of the pN1 or pN2 group [13]. Patients (any T stage) with N1 disease have a 5-year overall survival rates from 27.2% to 67% [2, 7, 32]. To better analyze the accurate prognosis of stage N1 disease, some studies subdivide N1 disease into hilar N1 (station 10), interlobar N1 (station 11), and peripheral N1 (stations 12 to 14) or single-station N1, multiple-station N1. The 5-year survival rates for patients with hilar N1, interlobar N1, peripheral N1 were 19.7%, 39.8%, and 59.7%, respectively, which show a significant survival difference among these three groups. Patients with peripheral N1 have a favorable survival times compared with patients with hilar N1 metastasis (P = 0.02) [2, 7, 32]. Multiple-stations of lymph node metastasis have been known to be a poorer prognosis for survival rates [7, 10, 13, 28, 29, 33]. The survival time for hilar N1 patients is similar to the pT1-2N2M0 patients with resection (19.7% vs 32.1%, P = 0.2269) [29]. The hilar N1 patients have a high occurrence of multiple-station metastasis (74.7%) [34], which might be well to explain the above result. It also reports that the postoperative pN1 group tends to have loco-regional recurrence (37.0%) [13]. Furthermore, Demir A et al. [7] consider right lobe tumors have no statistical difference from left lobe tumors in the 5-year survival times (P = 0.64), while Riquet M et al. [10] suggest that N1 patients on the right side tended to show favorable prognosis. Whether the difference of the 5-year survival times on both sides significant needs more explicitly procedures to address this confusion.

N2 NSCLC as a mixture of heterogeneous stages.

The N2 disease has been known to be heterogeneous and there should debate when it comes to the appropriate treatment strategy. Several research institutions have made great explorations about prognosis, survival, treatments in N2 disease, studies concerning such as a single-station N2 disease vs a multiple-station N2 disease, unsuspected, occult or incidental N2 disease, minimal N2 vs bulky N2 disease, clinical N2 (cN2) vs pathological N2 (pN2) disease, skip metastasis (negative N1 and positive N2 disease), the number of involved lymph nodes [13]. Therefore, the overall 5-year survival has been reported to vary greatly. Considering the limited preoperative clinical staging with imaging modalities, numerous studies have demonstrated that there are some differences between the clinical staging and the pathologic staging. Robert J et al. [13] make a retrospective study to discover that the unsuspected N2 disease has common lymph node station in station 4R (36% of patients) followed by station 5, 6 (32% of patients). The incidence of unsuspected N2 disease after surgical resection is 14.5% to 18.5% [36]. Interestingly, there is no significant difference on the 5-year disease free survival and the overall survival between the patients with unsuspected N2 and the patients with pathological N1 disease, while pN2 disease shows a trend toward worse survival than pN1 disease on account of a high distant recurrence (47.8%) [13]. The primary tumor station and the mediastinal node metastasis station play a relevant role in determining the optimal management strategy, such as chemo-radiotherapy or the surgical resection, and accurate prediction of prognosis for cN2 disease. So, it is better to discuss the difference for the subdivision of cN2 disease. Matsunaga T et al. [31] classify cN2 lymph nodes into cN2a and cN2b, based on the location of the primary tumor and nodes involved. The cN2a group is the main upper lobe tumor with an upper mediastinal lymph node (UMLN) metastasis or the main lower lobe tumor with a lower mediastinal lymph node (LMLN) metastasis. The cN2b group is the main upper lobe tumor with a lower mediastinal lymph node (LMLN) metastasis or the main lower lobe tumor with an upper mediastinal lymph node (UMLN) metastasis. The cN2a group appears to have a more favorable survival than the cN2b group (29.6 vs 0%, P < 0.001), supporting those of previous reports that the upper lobe tumors show better survival compared with the lower lobe tumors from another aspect. What's more, the results as well as agree with that the radical resection is acceptable for the cN2a group though many studies indicate that surgery is not unfavorable for c-stage IIIA-N2 NSCLC on account of a high incidence of incomplete resection [31, 37, 38]. Similarly, Baba T et al. [15] classify pN2 lymph nodes into the pN2a-1 and the pN2a-2 groups according to the distance from mediastinal node station. The pN2a-2 group with the further mediastinal node station shows a worse survival than the pN2a-1 group with the nearer mediastinal node, due to

the higher multiple station metastases involvement and pneumonectomy. Together, these results suggest that the primary tumor station and the mediastinal node metastasis station have a close contact with prognosis of survival.

Whether or not surgery therapy has a survival benefit for cN2/pN2 NSCLC patients has been the focus of much attention. For previous decades, surgery for cN2/pN2 patients has low 5-year survival rate (10%) attributed to a high incidence of incomplete resection and early recurrence in distant organs. Therefore, many scholars suggest that surgery is not suitable for cN2/pN2 patients [37]. However, with rapid improvements of diagnostic facilities and the technology of surgery, the survival rates may be well promoted. Whether taking surgery therapy into account or not should be depended on the definite N2 disease. Initial surgery is expected to be a more promising strategy for the single-station cN2 patients and the single-station pN2 with negative subcarinal involvement patients whereas some find discontented 5 year overall survival of 23.6% with heterogeneous prognoses [37]. However, with respect to bulky N2 with short radius more than 2 cm or multiple-station N2 disease, pure surgery is not advocated [5, 10]. Comparing to minimal N2 metastases, bulky N2 metastases result in an unfavorable prognosis (P = 0.026) [10]. Concurrent chemo-radiotherapy, considered as the standard of care are mostly accepted because it shows a significant greater influence on local control in comparison with the chemotherapy [41-43]. Besides, patients with extensive mediastinal nodal metastasis and cN2 disease, involved in a poor survival rates, are suggested to receive chemo-radiotherapy [31, 44]. Finally, regarding the difficulty of complete staging N2 disease before surgery, some conservatively advocate that it is beneficial for neoadjuvant chemo-radiotherapy followed by surgery [45].

The survival differences still remain controversial between the single-station N2 disease and the multiple-station N2 disease or the single-zone N2 disease and the multiple-zone N2 disease. The single-station N2 disease differ from the single-zone N2 as well as the multiple-station N2 disease to the multiple-zone N2 disease. Kim MS et al. [28] find that single nodal zone involvement with squamous carcinomas is associated with a significantly superior survival rate over multiple zones (35.8% vs 17.4%), but there are no statistical differences between the two groups when referred to the adenocarcinomas (P = 0.23). Regarding to the patients with unsuspected N2 disease, there are no statistical differences between the single-zone metastasis group and the multiple-zone metastasis group in the 5-year disease free survival rates (P = 0.635) and the overall survival rates (P = 0.857) [28]. Matsunaga T et al. [31] discover there is no difference between single and multiple pN2 (P = 0.766), but a notable difference between single and multiple cN2 (P < 0.001). Because the clinical N2 is not always pathological N2. Patients who experience surgical resection with pN2 stage IIIA could classify into clinically N2 or N0-1 and pathological groups, and their survival curves are distinct [45, 46]. The above conflicting results may be attributed to the lack of consensus on the nodal description of the N2 disease and the complexity of the candidates' election. As compared with non-skip N2, patients with skip N2 have a better 5-year survival rate (40.2% vs 48.2% P = 0.03) [3], which is consistent with current reports [29, 46, 47].

Conclusion

Accurate staging is still considered as the most important prognostic factor and is closely associated with the most adequate treatment strategy in non-small cell lung cancer. The pT factor doesn't play a major role in the survival rate except in case of the T4 disease whereas the pN factor affects the prognosis of patients with NSCLC mostly. Whether the adjacent lobe invasion is regarded as T2 or T3 has not been reached consensus yet so far. Patterns of mediastinal lymph node metastases are associated with the location of the primary tumor. The primary tumor station and the mediastinal node metastasis station have a close contact with prognosis of survival. Patients with single station, skip metastasis and minimal N2 involved, show a favorable prognosis. On the contrary, patients with multiple-station or extensive mediastinal nodal metastasis and bulky N2 metastases are in relation with poor survival rates.

Acknowledgements

This work was supported by grants from the Youth Fund of Guangdong Medical College (xq1320).

Disclosure of conflict of interest

None.

Address correspondence to: Zhixiong Yang, Department of Oncology, Affiliated Hospital of Guangdong Medical University, 57 Renmin Road, Zhanjiang, PR China. E-mail: yangzhixiong068@126.com

References

[1] Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007; 57: 43-66.

[2] Rusch VW, Crowley J, Giroux DJ, Goldstraw P, Im JG, Tsuboi M, Tsuchiya R, Vansteenkiste J; International Staging Committee; Cancer Research and Biostatistics; Observers to the Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol 2007; 2: 603-12.

[3] Nakagiri T, Sawabata N, Funaki S, Inoue M, Kadota Y, Shintani Y, Okumura M. Validation of pN2 sub-classifications in patients with pathological stage IIIA N2 non-small cell lung cancer. Interact Cardiovasc Thorac Surg 2011; 12: 733-8.

[4] Saynak M, Hubbs J, Nam J, Marks LB, Feins RH, Haithcock BE, Veeramachaneni NK. Variability in defining T1N0 non-small cell lung cancer impacts locoregional failure and survival. Ann Thorac Surg 2010; 90: 1645-9; discussion 1649-50.

[5] Ma Q, Liu D, Guo Y, Shi B, Song Z, Tian Y. Surgical therapeutic strategy for non-small cell lung cancer with mediastinal lymph node metastasis (N2). Zhongguo Fei Ai Za Zhi 2010; 13: 342-8.

[6] Defranchi SA, Cassivi SD, Nichols FC, Allen MS, Shen KR, Deschamps C, Wigle DA. N2 disease in T1 non-small cell lung cancer. Ann Thorac Surg 2009; 88: 924-8.

[7] Demir A, Turna A, Kocaturk C, Gunluoglu MZ, Aydogmus U, Urer N, Bedirhan MA, Gurses A, Dincer SI. Prognostic significance of surgical-pathologic N1 lymph node involvement in non-small cell lung cancer. Ann Thorac Surg 2009; 87: 1014-22.

[8] Haam SJ, Park IK, Paik HC, Kim DJ, Lee DY, Lee JG, Bae MK, Chung KY. T-stage of non-small cell lung cancer directly invading an adjacent lobe. Eur J Cardiothorac Surg 2012; 42: 807-10; discussion 810-1.

[9] Wex P, Graeter T, Zaraca F, Haas V, Decker S, Bugdayev H, Ebner H. Surgical resection and survival of patients with unsuspected single node positive lung cancer (NSCLC) invading the descending aorta. Thorac Surg Sci 2009; 6: Doc02.

[10] Riquet M, Bagan P, Le Pimpec Barthes F, Banu E, Scotte F, Foucault C, Dujon A, Danel C. Completely resected non-small cell lung cancer: reconsidering prognostic value and significance of N2 metastases. Ann Thorac Surg 2007; 84: 1818-24.

[11] Detterbeck FC, Boffa DJ, Tanoue LT, Wilson LD. Details and difficulties regarding the new lung cancer staging system. Chest 2010; 137: 1172-80.

[12] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-4.

[13] Lee DH, Kim JB, Keum DY, Hwang I, Park CK. Long term survival of patients with unsuspected n2 disease in non-small cell lung cancer. Korean J Thorac Cardiovasc Surg 2013; 46: 49-55.

[14] Riquet M, Rivera C, Pricopi C, Arame A, Mordant P, Foucault C, Dujon A, Le Pimpec-Barthes F. Is the lymphatic drainage of lung cancer lobe-specific? A surgical appraisal. Eur J Cardiothorac Surg 2015; 47: 543-9.

[15] Baba T, Uramoto H, Kuwata T, Chikaishi Y, Nakagawa M, So T, Hanagiri T, Tanaka F. Survival impact of node zone classification in resected pathological N2 non-small cell lung cancer. Interact Cardiovasc Thorac Surg 2012; 14: 760-4.

[16] Meyers BF, Haddad F, Siegel BA, Zoole JB, Battafarano RJ, Veeramachaneni N, Cooper JD, Patterson GA. Cost-effectiveness of routine mediastinoscopy in computed tomography-and positron emission tomography-screened patients with stage I lung cancer. J Thorac Cardiovasc Surg 2006; 131: 822-9; discussion 822-9.

[17] Patterson GA, Piazza D, Pearson FG, Todd TR, Ginsberg RJ, Goldberg M, Waters P, Jones D, Ilves R, Cooper JD. Significance of metastatic disease in subaortic lymph nodes. Ann Thorac Surg 1987; 43: 155-9.

[18] Miura H, Taira O, Uchida O, Kato H. Invasion beyond interlobar pleura in non-small cell lung cancer. Chest 1998; 114: 1301-4.

[19] Riquet M, Berna P, Arame A, Mordant P, Das Neves Pereira JC, Foucault C, Dujon A, Le Pimpec Barthes F. Lung cancer invading the fissure to the adjacent lobe: more a question of spreading mode than a staging problem. Eur J Cardiothorac Surg 2012; 41: 1047-51.

[20] Ohtaki Y, Hishida T, Yoshida J, Ishii G, Kawase A, Aokage K, Nishimura M, Nagai K. The clinical outcome of non-small cell lung cancer patients with adjacent lobe invasion: the optimal

classification according to the status of the interlobar pleura at the invasion point. Eur J Cardiothorac Surg 2013; 43: 302-9.
[21] Yang HX, Hou X, Lin P, Yang H, Zeng CG, Rong TH, Fu JH. Peripheral direct adjacent lobe invasion non-small cell lung cancer has a similar survival to that of parietal pleural invasion T3 disease. J Thorac Oncol 2009; 4: 1342-6.
[22] Demir A, Gunluoglu MZ, Sansar D, Melek H, Dincer SI. Staging and resection of lung cancer with minimal invasion of the adjacent lobe. Eur J Cardiothorac Surg 2007; 32: 855-8.
[23] Verhagen AF, Schoenmakers MC, Barendregt W, Smit H, van Boven WJ, Looijen M, van der Heijden EH, van Swieten HA. Completeness of lung cancer surgery: is mediastinal dissection common practice? Eur J Cardiothorac Surg 2012; 41: 834-8.
[24] Dartevelle PG. Herbert Sloan Lecture. Extended operations for the treatment of lung cancer. Ann Thorac Surg 1997; 63: 12-9.
[25] Rice TW, Blackstone EH. Radical resections for T4 lung cancer. Surg Clin North Am 2002; 82: 573-87.
[26] Cerfolio RJ, Bryant AS. Distribution and likelihood of lymph node metastasis based on the lobar location of nonsmall-cell lung cancer. Ann Thorac Surg 2006; 81: 1969-73; discussion 1973.
[27] Shimada Y, Saji H, Kakihana M, Honda H, Usuda J, Kajiwara N, Ohira T, Ikeda N. Retrospective analysis of nodal spread patterns according to tumor location in pathological N2 non-small cell lung cancer. World J Surg 2012; 36: 2865-71.
[28] Kim MS, Lee HS, Lee JM, Zo JI, Lee GK, Nam BH. Prognostic value of single nodal zone metastasis in non-small-cell lung cancer. Eur J Cardiothorac Surg 2010; 38: 491-7.
[29] Matsuoka K, Sumitomo S, Misaki N. Prognostic factors in patients with pathologic T1-2N1M0 disease in non-small cell carcinoma of the lung. J Thorac Oncol 2007; 2: 1098-102.
[30] Misthos P, Sepsas E, Kokotsakis J, Skottis I, Lioulias A. The significance of one-station N2 disease in the prognosis of patients with nonsmall-cell lung cancer. Ann Thorac Surg 2008; 86: 1626-30.
[31] Matsunaga T, Suzuki K, Takamochi K, Oh S. Time to refine N2 staging? cN2alpha and cN-2beta based on local regional involvement provide a more accurate prognosis in surgically treated IIIA non-small-cell lung cancer than N2 alone or the number of node stations involved. Eur J Cardiothorac Surg 2014; 46: 86-91.
[32] Nakagawa T, Okumura N, Kokado Y, Miyoshi K, Matsuoka T, Kameyama K. Retrospective study of patients with pathologic N1-stage II non-small cell lung cancer. Interact Cardiovasc Thorac Surg 2007; 6: 474-8.
[33] Kang CH, Ra YJ, Kim YT, Jheon SH, Sung SW, Kim JH. The impact of multiple metastatic nodal stations on survival in patients with resectable N1 and N2 nonsmall-cell lung cancer. Ann Thorac Surg 2008; 86: 1092-7.
[34] Sawyer TE, Bonner JA, Gould PM, Foote RL, Deschamps C, Lange CM, Li H. Factors predicting patterns of recurrence after resection of N1 non-small cell lung carcinoma. Ann Thorac Surg 1999; 68: 1171-6.
[35] Cerfolio RJ, Bryant AS. Survival of patients with unsuspected N2 (stage IIIA) nonsmall-cell lung cancer. Ann Thorac Surg 2008; 86: 362-6; discussion 366-7.
[36] De Leyn P, Schoonooghe P, Deneffe G, Van Raemdonck D, Coosemans W, Vansteenkiste J, Lerut T. Surgery for non-small cell lung cancer with unsuspected metastasis to ipsilateral mediastinal or subcarinal nodes (N2 disease). Eur J Cardiothorac Surg 1996; 10: 649-54; discussion 654-5.
[37] Okada M, Tsubota N, Yoshimura M, Miyamoto Y, Matsuoka H. Prognosis of completely resected pN2 non-small cell lung carcinomas: What is the significant node that affects survival? J Thorac Cardiovasc Surg 1999; 118: 270-5.
[38] Yoshino I, Yoshida S, Miyaoka E, Asamura H, Nomori H, Fujii Y, Nakanishi Y, Eguchi K, Mori M, Sawabata N, Okumura M, Yokoi K; Japanese Joint Committee of Lung Cancer Registration. Surgical outcome of stage IIIA- cN2/pN2 non-small-cell lung cancer patients in Japanese lung cancer registry study in 2004. J Thorac Oncol 2012; 7: 850-5.
[39] Hishida T, Yoshida J, Ohe Y, Aokage K, Ishii G, Nagai K. Surgical outcomes after initial surgery for clinical single-station N2 non-small-cell lung cancer. Jpn J Clin Oncol 2014; 44: 85-92.
[40] Toker A, Tanju S, Ziyade S, Kaya S, Erus S, Ozkan B, Yilmazbayhan D. Alternative paratracheal lymph node dissection in left-sided hilar lung cancer patients: comparing the number of lymph nodes dissected to the number of lymph nodes dissected in right-sided mediastinal dissections. Eur J Cardiothorac Surg 2011; 39: 974-80.
[41] Tanner NT, Gomez M, Rainwater C, Nietert PJ, Simon GR, Green MR, Silvestri GA. Physician preferences for management of patients with stage IIIA NSCLC: impact of bulk of nodal disease on therapy selection. J Thorac Oncol 2012; 7: 365-9.
[42] Robinson LA, Ruckdeschel JC, Wagner H Jr, Stevens CW; American College of Chest Physicians. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132 : 243S-265S.

[43] Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, Kubik A, Krepela E, Fiala P, Pecen L. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 2004; 46: 87-98.

[44] Sun Y, Gao W, Zheng H, Jiang G, Chen C, Zhang L. Mediastinal lymph-nodes metastasis beyond the lobe-specific: an independent risk factor toward worse prognoses. Ann Thorac Cardiovasc Surg 2014; 20: 284-91.

[45] Andre F, Grunenwald D, Pignon JP, Dujon A, Pujol JL, Brichon PY, Brouchet L, Quoix E, Westeel V, Le Chevalier T. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol 2000; 18: 2981-9.

[46] Suzuki K, Nagai K, Yoshida J, Nishimura M, Takahashi K, Nishiwaki Y. The prognosis of surgically resected N2 non-small cell lung cancer: the importance of clinical N status. J Thorac Cardiovasc Surg 1999; 118: 145-53.

[47] Li J, Dai CH, Shi SB, Chen P, Yu LC, Wu JR. Prognostic factors and long term results of neo adjuvant therapy followed by surgery in stage IIIA N2 non-small cell lung cancer patients. Ann Thorac Med 2009; 4: 201-7.