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Re-appraisal of N2 disease by lymphatic drainage pattern for non-small-cell lung cancers: By terms of nodal *stations*, *zones*, *chains*, and *a composite*

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ABSTRACT

Purpose: N2 non-small-cell lung cancer (NSCLC) is a heterogeneous disease with an extremely wide range of 5-year survival rates. A composite method of sub-classification for N2 is likely to provide a more accurate method to more finely differentiate prognosis of N2 disease.
Methods: A total of 720 pN2 (T1-4N2M0) NSCLC cases were enrolled in our retrospective analysis of the proposed composite method. Survival rates were respectively calculated according to the N2 stratification methods: singly by "nodal stations", "nodal zones", or "nodal chains", or by combination of all three. Statistical analysis was carried out by Kaplan–Meier and Cox regression models.
Results: A total of 10,199 lymph nodes (8059 mediastinal; 2140 hilar and intra-lobar) were removed. By nodal station, there were 173 cases of single-station involvement and 547 multi-stations. By nodal zone, there were 413 single-zone involvement and 307 with multiple zones. By nodal chain, there were 311 cases with single-chain and 409 multi-chain involvements. The overall 5-year survival was 20% and median survival time was 27.52 months. The 5-year survival was significantly better for cases of single-zone involvement, as compared to multi-zones (29% *vs.* 6%, $p < 0.0001$). The 5-year survival rates of single- and multi-chains involvement were 36% and 8%, respectively ($p < 0.0001$). When taking all of the above grouping methods into consideration, the N2 disease state could be further sub-classified into two subgroups with respective survival rates of 36% and 7% ($p < 0.0001$). Subgroup I was composed of individuals with single-chain involvement and having either one or two station metastasis; individuals with any other metastasis combinations formed Subgroup II. Multivariate analysis revealed that the composite sub-classification method, number of positive lymph nodes, ratio of nodal metastasis, and pT information were the most important risk factors of 5-year survival.
Conclusions: By combining the three N2 stratification methods based on "stations", "zones", and "chains" into one composite method, prognosis prediction was more accurate for N2 NSCLC disease. Single nodal chain involvement, which may be either one or two nodal stations metastasis, is associated with best outcome for pN2 patients.

1. Introduction

Anatomical pulmonary resection combined with mediastinal lymph node dissection is standard practice for treating stages I and II non-small-cell lung cancers (NSCLCs). For N2-IIIa cases, the efficacy of this procedure remains a topic of debate. Since N2 NSCLC is characterized by a heterogeneous disease course and has an extremely wide range of survival post-surgical intervention (between 9% and 42%) [1–3], two opposite attitudes exist among thoracic surgeons. Resection of N2 has been largely abolished in western medical centers in response to negative results from clinical trials [4,5]; however, this procedure remains in practice throughout non-western regions. A balanced attitude on this topic assumes that a subgroup of N2-IIIa patients responds well to surgery and, thus, has favorable survival rates. Although much effort has been put forth recently to define this supposed subgroup [6], no definitive criteria have yet been established. To this end, it is first necessary to precisely stratify the N2 disease state in accordance with real postoperative survival rates.

Prior studies have shown that both the position and number (or positive ratio) of involved mediastinal lymph nodes were important risk factors of survival. Nodal positions were marked either by Naruke's mapping method [7], Mountain–Dresler's method [8], or by using the combined system from the International Association

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for the Study of Lung Cancer (IASLC) [10]. Based on these mapping methods, the extent of mediastinal lymph node metastasis is then normalized. The first prognosis staging method was suggested by Andre and colleagues [9]; four distinct situations of mediastinal nodal involvement were classified each among IIIA levels. IIIa-1 is defined as incidental findings of nodal metastases at a single station. IIIa-2 is single station involvement. IIIa-3 refers to multiple stations metastasis, and IIIa-4 is bulky or fixed multi-station N2 disease. A second system was proposed by IASLC in 2009, in which the concept of nodal "zones" was defined [10]. There were five mediastinal zones in total: supraclavicular zone, upper zone, AP zone, subcarinal zone and lower zone. Single zone involvement was associated with a significantly superior survival rate, as compared to that of multiple. Thirdly, Riquet's group [11] suggested that mediastinal nodal chains might also play a role in nodal spread of lung cancer and be closely related to prognosis. This proposal, however, has yet to be clinically verified.

Although the above three stratification methods (IIIA1–4 method, zones classification and chains definitions) have been occasionally referenced and are generally regarded as clinically relevant, no information about their inter-relationship was available. We hypothesized that these three stratification methods intersect in their utility for determining a patient's metastatic state and they will be complimentary for predicting survival of N2-III patients. Therefore, we sought to evaluate this hypothesis in the present study.

2. Patients and methods

Approval for the study was obtained from the Ethics Committee of the Hospital.

2.1. Patient population and operations

We reviewed the records of 3652 NSCLC patients who underwent major pulmonary resection at our institute (Department of Thoracic Surgery of Shanghai Pulmonary Hospital, China) between 1995 and 2005. All cases bearing pN2 disease (T1-4N2M0) were enrolled. The histopathological diagnosis of tumors was carried out in accordance with the 1999 World Health Organization guideline [12]. The database had previously (prior to March 2010) utilized Naruke's mapping method to describe mediastinal lymph node positions and the older version of TNM classification [7] for staging. Therefore, the nodal mapping information was first translated into the newer TNM language of the IASLC's system before being subjected to statistical analysis. The same procedure was applied to the T descriptions and the final pathologic staging [10].

All patients had undergone routine preoperative evaluations to exclude contraindications, including CT scan of the thorax, CT scan of upper abdomen or abdomen ultrasonography, fiberoptic bronchoscopy, brain CT or MRI scan and whole-body bone scintigraphy. Mediastinoscopies were only performed to exclude N3 disease in cases of suspected contra-lateral mediastinal lymphadenopathy. It is important to note that at our institute N2 disease with bulky mediastinal lymphadenopathy is generally considered contraindicative for surgery.

Complete resection was defined as removal of the primary pulmonary tumor and all accessible hilar and mediastinal lymph nodes, with no residual tumor left behind (resection of all macroscopic tumor and resection margins verified by frozen section examinations as free of tumor). Standard major lung resections, including (bi-)lobectomies, sleeve lobectomies, and pneumonectomies were performed. The criteria of systemic lymphadenectomy were defined as the removal of at least three mediastinal stations and a total of more than six lymph nodes, as previously described [13].

The exclusion criteria for the study included the following: patients bearing metastatic pulmonary carcinomas or small cell lung cancers, prior history of induction chemo- or radio-therapy, exploratory thoracotomy, palliative resection, and massive pleural dissemination. Final enrollment was composed of a total of 720 pN2 cases.

2.2. Follow-up and data collection

All patients were routinely followed-up once every three months for the first two years after the surgical intervention, and every six months thereafter. The choice of telephone interviews, mail or direct outpatient clinic visits were offered to each subject. A trained staff member collected information for survival and cause of death during each follow-up session. The end-point of follow-up was date of death or May 1, 2010; the mean follow-up period was 34 months (range: 7–142 months). Information of 668 patients was completed (92.7%), while 52 of the cases (7.3%) were lost to follow-up. Data concerning patients' demographics, blood and clinical findings, co-morbidities, operative methods, complications, pathological findings, and adjuvant treatments were recorded and included in statistical analysis.

2.3. Groupings

(1) Study groups by *stations*. Dr. Andre and associates had previously defined four subclasses of N2 as IIIA1–4. Since no preoperative mediastinal nodal histological examination had been performed on our patients, condition of IIIA-1 was not recorded in the database. Thus, we considered those patients as IIIA-2. In addition, there were no IIIA-4 cases by reason of contraindication. Therefore, a total of 173 IIIA-2 (single-station involvement) and 547 IIIA-3 (multi-station involvement) cases were included in our study cohort.
(2) Study groups by *zones*. In accordance with the proposal from the IASLC staging project, all N2 cases were divided between two groups: single- or multiple-involved mediastinal zones. Four intra-thoracic mediastinal nodal zones have been defined: upper zone/superior mediastinal nodes (station-2, -3 and -4); AP zone/aortic nodes (station-5 and -6); subcarinal zone (station-7) and lower zone (station-8 and -9). Station-1 nodes are defined as belonging to the supraclavicular zone and are beyond the reach of thoracotomy procedures (Fig. 1A).
(3) Study groups by *chains*. As suggested by Dr. Riquet's group, five intra-thoracic mediastinal lymphatic chains were classified as follows: Stations -2 and -4; Stations-3A and -3P; Stations-5 and -6; Station-7; Stations-8 and -9. The chain composed of Station-1 nodes was contraindicated for surgery as described (Fig. 1B).

2.4. Statistical analysis

Statistical analysis was performed by the chi-square test for categorical variables and Student's *t*-test for continuous variables. The survival rate was calculated according to the Kaplan–Meier and the life-table methods. Differences among survival rates were compared by log-rank and pairwise Wilcoxon test. Multivariate analysis for censored data was performed using a Cox regression model. All statistical analysis was performed on SPSS version 15.0 software. The mean shrinkage (95% confidence interval) was calculated. Differences were considered to be significant when p-value was less than 0.05.