Results of surgical intervention for p-stage IIIA (N2) non-small cell lung cancer: Acceptable prognosis predicted by complete resection in patients with single N2 disease with primary tumor in the upper lobe

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Objectives: Non-small cell lung cancer with mediastinal lymph node involvement is a heterogeneous entity different from single mediastinal lymph node metastasis to multiple nodes or extranodal disease. The objective of this study was to identify the subpopulation of patients with N2 disease who can benefit from surgical intervention.

Methods: We reviewed 219 consecutive patients with N2 non-small cell lung cancer treated with a thoracotomy between November 1980 and June 2002 and retrospectively analyzed 154 of those who had p-stage IIIA disease and underwent a complete resection. Age, sex, side (right or left), histology, location (upper or middle-lower lobe), tumor size, c-N factor, and N2 level (single or multiple) were used as prognostic variables.

Results: The 3- and 5-year survivals were 45.3% and 28.1%, respectively, in patients with p-stage IIIA (N2) disease. Survival for those with single N2 non-small cell lung cancer was significantly better than in those with multiple N2 disease ($P = .0001$), and patients with a tumor in the upper lobe showed a significantly longer survival than those with middle-lower lobe involvement ($P = .0467$). The 3- and 5-year survivals for patients with single N2 disease with a primary tumor in the upper lobe were 74.9% and 53.5%, respectively. A multivariate analysis with Cox regression identified 5 predictors of better prognosis: younger age, squamous cell carcinoma as determined by histology, primary tumor location in the upper lobe, c-N0 status, and a single station of mediastinal node metastasis.

Conclusion: Our results suggest that of the heterogeneity of N2 diseases, patients with single N2 disease with non-small cell lung cancer in the upper lobe are good candidates for pulmonary resection.

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Non-small cell lung cancer (NSCLC) with ipsilateral mediastinal lymph node metastasis is generally considered to be a locally advanced disease resulting in a poor outcome, although these patients can be divided into heterogeneous subpopulations, such as those with bulky extranodal metastases and those with either multiple or single N2 involvement. Among these patients, a proportion of patients with N2 disease, including surgically discovered patients with positive nodes, have been treated with pulmonary resection. The overall 5-year survival in patients with N2 disease who underwent a curative resection has been

reported to range from 19% to 36%; however, most retrospective studies of surgical results of treated patients with N2 NSCLC were highly selective.¹ Furthermore, several prognostic factors have recently been defined by historical studies, which have shown that complete resection, single mediastinal node metastasis, c-N0-1, low p-T factor, and small tumor size are predictors of better prognosis in patients with N2 NSCLC.²⁻⁵ However, the type of patients with N2 NSCLC who can benefit most from a thoracotomy has not been clarified. We retrospectively studied patients with N2 NSCLC treated at our institute by analyzing prognostic factors to identify subpopulations with good operative indications.

Patients and Methods

Patients

The records of all 219 patients with NSCLC who underwent a thoracotomy and were confirmed to have positive mediastinal nodes between November 1980 and June 2002 at Toneyama National Hospital, Osaka, Japan, were reviewed. Three patients died of postoperative complications and were excluded from the present study. In principle, we considered patients with single N2 disease to be resectable and those with extranodal or bulky mediastinal node involvement or multiple N2 disease to be inoperable. Thus 163 patients underwent a complete resection (154 for p-stage IIIA, 8 for p-stage IIIB, and 1 for p-stage IV), and an incomplete resection and exploratory thoracotomy were performed in 28 patients for each.

In the present study we focused on the 154 patients with p-stage IIIA (N2) disease treated with a complete resection (Table 1). Follow-up was complete in 131 patients, and the median time for follow-up of all patients was 111.2 months. The mediastinal lymph node was pathologically confirmed to be metastatic in all patients who underwent a pulmonary resection. Preoperative diagnosis was performed by using chest radiography and computed tomographic (CT) imaging, as well as fiberoptic bronchoscopy for pulmonary nodules. Mediastinal nodes larger than 1 cm in the short axis were defined as clinical N2 disease. A mediastinoscopy was carried out in selected patients because of protocol setting or in some with suspected c-N2 disease before induction therapy, although not routinely. Brain CT or magnetic resonance imaging results, as well as those from upper abdominal CT and bone scintigraphy examinations, were used to detect distant metastases. Postoperative staging was performed according to the 1997 TNM classification.⁶ All dissected hilar and mediastinal lymph nodes were pathologically examined and classified according to anatomic location by using Naruke's numbering system.⁷ Complete resection was defined as that without a macroscopic residual lesion and with microscopic free margins around the tumor site. Patients with pleural dissemination or malignant pleural effusion were defined as having an incomplete resection, even if there was no macroscopic residual lesion after the pulmonary resection. Induction and adjuvant therapy were performed in 22 and 46 patients, respectively. Eighty-six patients were treated with surgical intervention alone. All patients treated with induction therapy had been given a diagnosis of c-N2 disease on the basis of CT scanning or mediastinoscopy. As for lymph node dissection, in patients with a tumor

TABLE 1. Characteristics of 154 patients with p-stage IIIA (N2) NSCLC (from our patient database: November 1980-June 2002)

Age (y)	38–80 (median, 62)
Sex	
Female	55
Male	99
c-N factor	
c-N0	71
c-N1	20
c-N2	60
c-N3	3
N2 level	
Single	75
Multiple	79
Histology	
Ad	101
Sq	41
La	11
Ad-Sq	1
Side	
Right	99
Left	55
Treatment	
Surgical intervention alone	86
Surgical intervention + CT	39
Surgical intervention + RT	11
Surgical intervention + CRT (Induction therapy, 22)	18
Mode	
Pneumonectomy	25
Lobectomy	126
Partial resection	3

Ad, Adenocarcinoma; *Sq*, squamous cell carcinoma; *La*, large cell carcinoma; *Ad-Sq*, adenosquamous cell carcinoma; *CT*, chemotherapy; *RT*, radiation therapy; *CRT*, chemoradiation therapy.

in the right upper-middle lobe, the superior mediastinal, paratracheal, pretracheal, tracheobronchial, and subcarinal nodes were removed. In those with a tumor in the left upper lobe, the tracheobronchial, subaortic, para-aortic, and subcarinal nodes were removed. In addition to these nodes, paraesophageal and pulmonary ligament nodes were dissected in patients with tumors in both lower lobes. The pretracheal node in patients with a left-side tumor and the anterior and posterior mediastinal nodes were optional.

Patients were evaluated on the basis of age, sex, side (right or left), histology, tumor location (upper lobe or middle-lower lobe), largest diameter of the tumor, c-N factor, and metastatic mediastinal lymph node level (single or multiple) to determine prognostic factors.

Statistical Analysis

Overall survival denotes the period from the date of initial treatment. The probability of survival was calculated by using the Kaplan-Meier method.⁸ The prognostic influence of variables on survival was analyzed by using a log-rank test and a Cox proportional hazards model.⁹

Figure 1. Overall survival for 154 patients with p-stage IIIA (N2) NSCLC who underwent a complete resection.

Results

The 3- and 5-year survivals for patients with p-stage IIIA (N2) disease who underwent a complete resection were 45.3% and 28.1%, respectively (Figure 1). The 5-year survivals for patients with c-N0, c-N1, and c-N2-3 disease were 45.5%, 26.5%, and 12.0%, respectively. The survival of patients with c-N0 disease was significantly better than that of patients with c-N2-3 disease ($P < .0001$). No significant difference was found between the c-N0 and c-N1 groups ($P = .2249$). Median survival time (MST) was 49.5 months for the c-N0 group, 37.7 months for the c-N1 group, and 17.9 months for the c-N2-3 group. Thus preoperative c-N factor, determined with a chest CT scan, was able to predict prognosis because surgically discovered patients with N2 disease had a better outcome than those given a preoperative diagnosis of c-N2 disease.

We also assessed survival by histologic type. The 5-year survival and MST were 39.6% and 46 months, respectively, for patients with squamous cell carcinoma; 23.9% and 30.6 months, respectively, for patients with adenocarcinoma; and 18.2% and 15.4 months, respectively, for patients with large cell carcinoma. We found a significant difference between patients with squamous cell carcinoma and those with large cell carcinoma ($P = .0200$). Furthermore, the survival for patients with squamous cell carcinoma showed a tendency to be better than that for patients with adenocarcinoma, although the difference was not significant ($P = .0826$).

In the present study a single metastasis in the mediastinal node was retrospectively found in 75 patients, and multiple metastases were found in 79 patients. The 5-year survival and MST for patients with single N2 disease were 42.7% and 48.5 months, respectively, which were both significantly better than those seen in the multiple N2 group, which had a 5-year survival of 15.5% and MST of 23.6 months (Figure 2). The outcome for patients with multiple N2 disease who underwent a complete resection was poor, although it was better than that for patients treated with an incomplete resection, who had an MST of 14.2, or those

Figure 2. Probability of survival for patients with stage IIIA (N2) NSCLC who underwent a complete resection according to N2 level. Survival for those with single N2 disease was significantly better than for those with multiple N2 disease.

with exploratory thoracotomy, who had an MST of 13.9 months.

We speculated that patients with single N2 disease with a primary lesion in the upper lobe tended to survive longer than patients with other types of N2 disease, and therefore we studied survival difference on the basis of tumor location. The 5-year survival and MST for patients with a tumor in the upper lobe were 34.6% and 37.7 months, respectively, which were significantly better than those for patients with a lesion in the middle-lower lobe (Figure 3).

When analyzed according to both N2 level and tumor location (upper or middle-lower lobe), the 3- and 5-year survivals were 74.9% and 53.5%, respectively, and MST was 124 months in patients with single N2 disease and an upper lobe primary tumor, which were significantly better than the results for patients with multiple N2 disease (Figure 4). Metastatic mediastinal lymph nodes in single N2 NSCLC are listed in Table 2 according to tumor location. Lesions in the upper lobe were mainly metastasized to the upper mediastinal nodes, and those in the middle-lower lobe were mainly metastasized to the subcarinal nodes. We further analyzed patients with single N2 disease with an upper lobe lesion to investigate outcome by side. The 5-year survival was 70.0% in patients with a left upper lobe lesion involving a subaortic or para-aortic lymph node ($n = 10$) and 55.4% in patients with a right upper lobe lesion involving a superior mediastinal, paratracheal, pretracheal, or tracheobronchial node ($n = 22$, $P = .5095$). Although the number of patients was small, the 5-year survival of those with a left upper lobe lesion was extremely good.

A univariate analysis using the variables listed in Table 3 showed that histology (large cell carcinoma/squamous cell carcinoma), location (middle-lower lobe/upper lobe), tumor diameter, c-N factor (c-N2-3/c-N0), and N2 level (multiple/single) were significant prognostic factors. Patient age also

Figure 3. Probability of survival for patients with stage IIIA (N2) NSCLC who underwent a complete resection according to primary tumor location. Two patients with a tumor in the left main bronchus were excluded from these results. Patients with a tumor in the upper lobe showed a significantly longer survival compared with that in those with a tumor in the middle-lower lobe.

Figure 4. Probability of survival for patients with stage IIIA (N2) NSCLC who underwent a complete resection according to both N2 level and tumor location. Two patients with a tumor in the left main bronchus were excluded from these results. The survival of patients with single N2 disease and upper lobe primary involvement was significantly better compared with that of those with multiple N2 disease and upper lobe primary involvement ($P = .0010$) or those with multiple N2 disease and middle-lower lobe primary involvement ($P < .0001$) and also tended to be better than survival in patients with single N2 disease and middle-lower lobe primary involvement ($P = .0900$).

showed a prognostic factor trend, although it was not significant, whereas sex and tumor side did not have a prognostic effect. Using these variables, we also performed a multivariate analysis (Table 4). We found that age, histology (both adenocarcinoma and large cell carcinoma/squa-

TABLE 2. Prevalence of mediastinal positive lymph nodes according to location of the primary lesion in patients with single N2 p-stage IIIA NSCLC

Station no.	RUL	LUL	RMLL	LLL
1	1		1	
2	2			
3	13	1	1	1
3a	3	1	2	
3p		1	1	
4	6	1	2	
5		7		1
6		3		
7	2	1	13	5
8	1		1	1
9				2

Station, Mediastinal lymph node station according to Naruke's numbering system⁷; RUL, right upper lobe; LUL, left upper lobe; RMLL, right middle-lower lobe; LLL, left lower lobe.

TABLE 3. Potential prognostic factors in patients with p-stage IIIA (N2) NSCLC by univariate analysis

Variables	Hazard ratio	95% CL	P value
Age	1.024	0.999-1.050	.0618
Sex (male/female)	1.198	0.790-1.817	.3958
Side (right/left)	1.055	0.700-1.590	.7975
Histology			
Sq	1.000		
Ad	1.531	0.951-2.464	.0794
La	2.517	1.201-5.273	.0145
Location (ML/U)	1.490	1.003-2.216	.0484
Tumor size	1.153	1.011-1.315	.0331
c-N			
N0	1.000		
N1	1.453	0.779-2.709	.2399
N2-3	2.807	1.812-4.348	<.0001
N2 (multiple/single)	2.189	1.455-3.293	.0002

CL, Confidence limit; Sq, squamous cell carcinoma; Ad, adenocarcinoma; La, large cell carcinoma; ML, middle-lower lobe; U, upper lobe.

mous cell carcinoma), location (middle-lower lobe/upper lobe), c-N factor (c-N2-3/c-N0), and N2 level (multiple/single) were independent prognostic predictors.

Discussion

Surgical indication for a patient with N2 NSCLC is generally marginal because of local advancement and poor prognosis; however, it has recently been reported that a proportion of patients with N2 NSCLC might have a good chance of survival after a pulmonary resection.^{2,4,5,10} Although several potential prognostic factors have been tested, it is still unclear which of these patients might benefit most from surgical intervention. In the present study we retrospectively analyzed patients with p-stage IIIA (N2) disease in

TABLE 4. Potential prognostic factors in patients with p-stage IIIA (N2) NSCLC by multivariate analysis

Variables	Hazard ratio	95% CL	P value
Age	1.034	1.009-1.060	.0066
Sex (male/female)	1.423	0.901-2.247	.1306
Side (right/left)	1.015	0.657-1.568	.9469
Histology			
Sq	1.000		
Ad	3.048	1.710-5.432	.0002
La	7.328	3.083-17.416	<.0001
Location (ML/U)	1.578	1.030-2.419	.0362
Tumor size	1.111	0.955-1.293	.1713
c-N			
N0	1.000		
N1	1.563	0.764-3.194	.2210
N2-3	3.028	1.842-4.978	<.0001
N2 (multiple/single)	1.883	1.208-2.936	.0052

See abbreviations in Table 3.

our institute to identify subpopulations suitable for pulmonary resection, and our results indicated that patients with single N2 involvement with NSCLC in the upper lobe would be good candidates for a possible curative resection.

We expected that survival for patients with single N2 disease would be significantly better than that for those with multiple N2 disease (Figure 2) because the latter is definitively an advanced status, and other reports have shown a significantly better survival in such patients with N2 NSCLC.^{2-5,11-17} Furthermore, Luzzi and associates¹⁸ noted that patients with less than 50% lymph node infiltration, which was calculated as the ratio of positive nodes to all dissected mediastinal nodes, showed a significantly more favorable outcome. We believe that those results are important when considering surgical indications in patients with N2 NSCLC because patients with single and multiple N2 disease are heterogeneous subpopulations that have very different prognoses. The 5-year survival of 42.7% and MST of 48.5 months for patients with single N2 NSCLC in the present study suggest that patients with less advanced N2 NSCLC could be cured by, or at least benefit from, surgical resection.

It was interesting to note differences in survival of patients with N2 NSCLC by location of the primary tumor (upper vs middle-lower lobe, Figure 3). When analyzing only patients with single N2 disease with a tumor in the upper lobe, the 5-year survival was 53.5% (Figure 4), which was somewhat surprising because it was similar or better than that reported for N1 NSCLC.^{6,19} Because we found no survival difference by location of the primary lesion in patients with p-N0 or pN1 NSCLC in our institute (data not shown), a better prognosis for patients with an upper lobe lesion was an interesting characteristic of N2 NSCLC disease. Ichinose and colleagues⁵ pointed out the relationship

between primary tumor location and metastatic N2 station (ie, there were frequent metastases from the right upper lobe at no. 3, from the left upper lobe at no. 5, and from the right middle-lower and left lower lobes at no. 7). In the present study we also observed a similar tendency of prevalent positive nodes (Table 2). Furthermore, the outcome of N2 NSCLC associated with upper mediastinal lymph node involvement has been reported to be better compared with that with lower mediastinal metastasis.^{10,11,20} Thus we suppose that there is a relationship between upper mediastinal node involvement and a tumor located in the upper lobe and, furthermore, that this particular subpopulation could benefit from complete resection. We also propose that a prethoracotomy evaluation by tumor location provides more information to predict the prognosis of patients than that by site of metastatic node.

Patients with c-N0 status showed significantly better survival than those with c-N2-3 status (Tables 3 and 4). This result has also been shown in other studies, and c-N diagnosis using chest CT scanning is an important reference factor.^{2,4,10,15} However, it has been reported that lymph node size detected on the basis of CT is not reliable for an evaluation of metastasis.²¹ Therefore we propose that a more accurate evaluation for mediastinal lymph nodes is necessary. We recently adopted fiberoptic transbronchial needle aspiration, mediastinoscopy, and/or exploratory thoracoscopy for preoperative evaluation of patients with c-N2 disease given a diagnosis on the basis of chest CT scanning. Although fluorodeoxyglucose-positron emission tomography might be useful in the evaluation of mediastinal nodes, the accuracy is still less than that of mediastinoscopy.^{22,23} Thus we believe that accurate preoperative staging with these examinations can contribute to the decision of surgical indication and better prognosis for patients with less advanced N2 NSCLC.

Univariate and multivariate analyses showed that histologic type was one of the prognostic factors in completely resected stage IIIA (N2) NSCLC (Tables 3 and 4). Furthermore, the outcome of patients with squamous cell carcinoma was significantly better than that of those with adenocarcinoma or large cell carcinoma in the present study. A better survival in patients with squamous cell carcinoma compared with those with nonsquamous cell carcinoma was previously mentioned by Vansteenkiste and colleagues¹⁵ and Goldstraw and associates¹⁶ with significant differences, whereas Suzuki and coworkers,² Martini and colleagues,¹⁰ and Nakanishi and associates²⁰ found no significant results by histologic type. In their studies Suzuki and coworkers² and Nakanishi and associates²⁰ compared adenocarcinoma with other histologic findings, which were mainly squamous cell carcinoma; however, they also included large cell carcinoma and adenosquamous cell carcinoma, which are generally considered to be more malignant in patients with

NSCLC.²⁴ In contrast to our report, Martini and colleagues¹⁰ did not perform a multivariate analysis. From their and our results, we considered that squamous cell carcinoma histology is a better prognostic predictor in addition to single N2 status and tumor location in the upper lobe in patients with p-stage IIIA (N2) NSCLC.

A portion of the patients (22/154) in the present study were treated with induction therapy, and their outcome also depended on the status of persistent N2.²⁵⁻²⁷ Regarding the level of mediastinal node metastasis, Sawabata and coworkers²⁸ recently clarified that the chance of 5-year survival was 54% for single-level and 11% for multiple-level persistent N2 disease after induction therapy. These findings are similar to the results in the present study.

The Toronto group reported that patients with a lesion in the right upper lobe frequently had upper mediastinal node involvement, suggesting a direct lymphatic drainage mechanism from the primary tumor to the right paratracheal or tracheobronchial lymph nodes.²⁹ Later, they also reported that good prognosis could be predicted after complete resection in patients with a primary tumor in the left upper lobe associated with only subaortic node involvement.³⁰ Our results are compatible with the results of those reports, and we additionally clarified 2 new findings in the present study, which were that single N2 involvement, upper lobe tumor, and histology of squamous cell carcinoma were better independent prognostic predictors by means of multivariate analysis in patients with N2 NSCLC, and the 5-year survival of patients with single N2 NSCLC with an upper lobe tumor was similar to that of patients with N1 NSCLC and better than results of previous reports.

In summary, younger age, squamous cell carcinoma histology, tumor in the upper lobe, single N2 NSCLC, and c-N0 status on a chest CT scan were better independent prognostic predictors. Among the heterogeneous entities, we considered that a patient with a single N2 NSCLC in the upper lobe is the best candidate for pulmonary resection.

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