

Prognostic Factors in Patients with Pathological and N2 Non-Small Cell Lung Cancer

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Although a general consensus concerning surgical treatment of N2 non-small cell lung cancer (NSCLC) patients has not yet been obtained, survival of such patients not treated surgically is extremely limited. Recently 5-year survival rates of 8 to 36% have been reported in completely resected N2 NSCLC with systemic mediastinal lymph node dissection.¹⁻¹²⁾ According to those reports, a certain population of N2 patients apparently benefits from surgery. Among the pathological N2 (pN2) cases who underwent surgery, relatively favorable prognostic factors were complete resection,²⁻⁵⁾ low clinical N factor,¹⁻⁴⁾ low T factor,²⁻⁷⁾ and also low metastatic mediastinal lymph node station.²⁻¹²⁾

We retrospectively evaluated pathological patients who underwent complete resection to identify and evaluate prognostic factors. Between 1990 and 2001, among 1,095 consecutively treated patients with non-small lung cancer who underwent complete resection, including systemic mediastinal lymph node dissection, there were 214 pN2 patients. In this period, chest computed tomography (CT), brain CT, abdominal ultrasonography, and bone scintigram were routinely performed before surgery to evaluate extent of disease. Although mediastinoscopy was not performed, bulky N2 tumors revealed by chest X-ray or chest CT were regarded as inoperable. In preoperative clinical evaluation, lymph nodes 1.0 cm or larger in the shortest axis on CT were considered metastatic. Induction therapy was not performed in this period especially for patients in whom complete resection was anticipated. Lymph nodes were numbered according to the lymph node mapping reported by Naruke and associates⁷⁾ and the American Joint Committee on Cancer.⁸⁾

The overall 5-year survival rate of 214 patients with pN2 NSCLC using the Kaplan-Meier method was 25%. Among 15 clinicopathological factors of pN2 patients,

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there was no significant difference of 5-year survival in according to 9 factors including gender, age, histology of the tumor, the side operated on, the lobe in which the tumor was located, surgical method, subcarinal lymph node metastasis, vascular invasion and lymphatic invasion. On the other hand, 24 patients (11%) with a tumor 2.0 cm or less in size had a 66% 5-year survival rate whereas that of 190 patients (89%) with a tumor greater than 2.0 cm in size was 21%. This difference was statistically significant ($p=0.0122$). In addition to the tumor size, there were significant differences in 5-year survival rate according to 5 other factors, i.e. clinical T factor ($p=0.0122$), pT factor ($p=0.002$), clinical N factor ($p=0.040$), N1 station metastasis ($p=0.0450$) and N2 station metastasis ($p=0.0106$). Pathological N2 patients included 42% of patients with clinical N0 disease and 11% of patients with clinical N1 disease, who had 30% and 34% 5-year survival respectively. However, the 47% of patients with clinical N2 disease had only a 14% 5-year survival. Among those 6 prognostic factors, multivariable analysis by means of Cox's proportional hazards model indicated only one independent prognostic factor, that of pT ($p=0.0447$).

Although surgery for N2 lung cancer is highly controversial, a 5-year survival rate of more than 30% was reported in pN2 disease cases carefully selected for surgery.^{2,7,8,10)} Among surgical cases of pN2 disease, several prognostic factors were evaluated, including complete resection of tumor, TNM factor, surgical method, histological type, metastasis station site of mediastinal lymph node and number of metastatic stations.¹⁻¹²⁾ The majority of these factors were postoperative pathologic factors, except for the clinical TNM factor. In surgically treated pN2 patients, the clinical N factor was regarded as a significant prognostic factor. Cases estimated as to be clinical N2 showed a significantly worse outcome than clinical N0-1 cases.^{1-4,8-10)} In our study, gender, age and histological type of tumor showed no correlation with 5-year survival rate in both subgroups, as reported in many other reports.¹⁻¹⁰⁾ Tumors 2.0 cm or less in size consisted of about 10% of all N2 tumor in both subgroups, which also

agreed with other reports.^{8,10} In the pN2 group, patients with tumor 2.0 cm or less in size had a significantly better 5-year survival rate (66%, $p=0.0122$) than those (21%) with tumors over 2.0 cm. Pathological and clinical T factors were significant prognostic factors, while patients with T1–2 tumors had longer survival than those with T3–4 tumors, which agrees with other reports.^{2–7} In pN2 group, 90 patients (42%), 24 patients (11%), 92 patients (43%), and 8 patients (4%) were regarded as clinical N0, N1, N2, and N3, respectively, and their 5-year survival rates were 30%, 34%, 14%, and 0%, in which these differences were significant ($p=0.04$). Numbers of N1 station metastasis had prognostic significance in the pN2 group. No metastasis to an N1 station lymph node among the pN2 group means “skip metastasis.” In the present study skip metastasis occurred in 39% of pN2 cases and the patients with this phenomenon showed better survival than the patients with metastasis to N1 station nodes, as in other reports.¹⁰ The number of N2 station metastasis were related to a 5-year survival rate. Among the pN2 group, 51% of patients showed single metastasis and a 31% 5-year survival rate whereas 49% of patients showed multiple metastasis and an 18% 5-year survival rate. Subcarinal lymph node metastasis was recognized in 38% of pN2 patients although this had no prognostic significance. There were significant differences in a 5-year survival rate in relation to those 6 factors among pN2 patients, although multivariable analysis indicated only one independent prognostic factor, that of pT. However we could obtain preoperatively only 2 factors, including cT and cN, among the 6 prognostic factors. In spite of postoperative chemoradiotherapy to pN2 patients, a better outcome could not be obtained.¹⁰ Accurate preoperative diagnosis of nodal status should improve evaluation of operability of N2 patients. Although sensitivity and specificity of nodal status using a CT scan was 33–56% and 86–91%, respectively, positron emission tomography had 66–78% sensitivity and 81–86% specificity.^{11,12} Positron emission tomography and CT are more accurate than CT alone in detecting mediastinal lymph node metastases from NSCLC.¹²

References

1. Pearson FG, DeLarue NC, Ilves R, Todd TR, Cooper JD. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. *J Thorac Cardiovasc Surg* 1982; **83**: 1–11.
2. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. *Surg Clin North Am* 1987; **67**: 1037–49.
3. Watanabe Y, Shimizu J, Oda M, Hayashi Y, Watanabe S, et al. Aggressive surgical intervention in N2 non-small cell cancer of the lung. *Ann Thorac Surg* 1991; **51**: 253–61.
4. Vansteenkiste JF, De Leyn PR, Deneffe GJ, Stalpaert G, Nackaerts KL, et al. Survival and prognostic factors in resected N2 non-small cell lung cancer: a study of 140 cases. *Ann Thorac Surg* 1997; **63**: 1441–50.
5. Davtayan HG, Corno AF, Laks H, Bhuta S, Flynn WM, et al. Prognosis and survival in resected lung carcinoma based on the new international staging system. *J Thorac Cardiovasc Surg* 1988; **96**: 44–7.
6. Goldstraw P, Mannam GC, Kaplan DK, Michail P. Surgical management of non-small cell lung cancer with ipsilateral mediastinal node metastasis (N2 disease). *J Thorac Cardiovasc Surg* 1994; **107**: 19–28.
7. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. Lobe-specific extent of systemic lymphnode dissection for non-small cell lung carcinomas according to a retrospective study of metastasis and prognosis. *J Thorac Cardiovasc Surg* 1999; **117**: 1102–11.
8. Mountain CF. Surgery for stage IIIa-N2 non-small cell lung cancer. *Cancer* 1994; **73**: 2589–98.
9. Suzuki K, Nagai K, Yoshida J, Nishimura M, Takahashi K, et al. 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.
10. Kim KJ, Ahn YC, Lim do H, Han J, Park K, et al. Analyses on prognostic factors following tri-modality therapy for stage IIIa non-small cell lung cancer. *Lung Cancer* 2007; **55**: 329–36.
11. Scott WJ, Gobar LS, Terry JD, Dewan NA, Sunderland JJ. Mediastinal lymph node staging of non-small-cell lung cancer: a prospective comparison of computed tomography and positron emission tomography. *J Thorac Cardiovasc Surg* 1996; **111**: 642–8.
12. Chin R Jr, Ward R, Keyes JW, Choplin RH, Reed JC, et al. Mediastinal staging of non-small cell lung cancer with positron emission tomography. *Am J Respir Crit Care Med* 1995; **152**: 2090–6.