Original Article

Survival and Prognostic Factors in Resected cN2-pN0 Non-small Cell Lung Cancer

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This study retrospectively examined the records of patients with clinical N2 (cN2) stage non-small cell lung cancer (NSCLC) who were surgically treated but who actually had pathologic N0 (pN0) stage disease. From 1982 to 1997, 94 patients with cN2 NSCLC underwent surgery. Forty-five patients proved to have pN0 disease, with an overall 5-year survival rate of 67.3%. According to the Cox model, visceral pleural invasion (p=0.01) and a carcinoembryonic antigen (CEA) concentration ≥2.5 ng/mL (p=0.03) negatively influenced survival. The six patients with both visceral pleural involvement and a CEA ≥2.5 ng/mL all died within five years compared with a 78.1% 5-year survival for the 21 patients who had neither factor. For the subgroup of patients who have poor prognostic factors, multimodality therapy should be considered.

Our previous report found that parietal pleural invasion, elevated CEA concentration, and the number of involved mediastinal lymph node (MLN) stations correlated with survival in 40 patients with cN2-pN2 disease who underwent resection. These data show how important it is to assess pleural status carefully and measure the CEA concentration, as is to determine the MLN status in patients with cN2 disease. (Ann Thorac Cardiovasc Surg 2004; 10: 9–13)

Key words: non-small cell lung cancer, clinical N2 stage disease, pathologic N0 stage disease, surgery, prognosis

Introduction

Surgery remains the treatment of choice for controlling pathologic grade N0 (pN0) non-small cell lung cancer (NSCLC). Although many patients achieve long-term survival, a significant proportion suffer local, regional or distant recurrence, and the 5-year survival rates after resection of pN0 disease range from 38% (T3N0) to 67% (T1N0).[1)] The use of multimodality therapy to treat early-stage NSCLC is now under investigation.[1,2)] Thus, surgeons need to be certain that the lesions are staged accurately to determine the most appropriate treatment plan. The problem is that although many prognostic factors have been described, many determinants cannot be known with certainty until after resection. Therefore, the identification of prognostic factors which can be determined pre- or at least intraoperatively is needed to individualize treatment for maximal efficacy.

We recently have identified prognostic factors in 40 patients with cN2-pN2 disease who underwent resection. We concluded that surgery prolongs survival in patients with cN2-pN2 disease only when specific favorable prognostic factors are present. This report focuses on prognostic factors which were determinable pre- or intraoperatively in 45 patients with cN2-pN0 disease who underwent resection. The role of surgery in this subgroup of patients is discussed.

Patients and Methods

Patients

From September 1982 to March 1997, 94 patients with a clinical diagnosis of N2 (cN2) NSCLC except for bulky cN2 underwent resection with curative intent at Hokkaido

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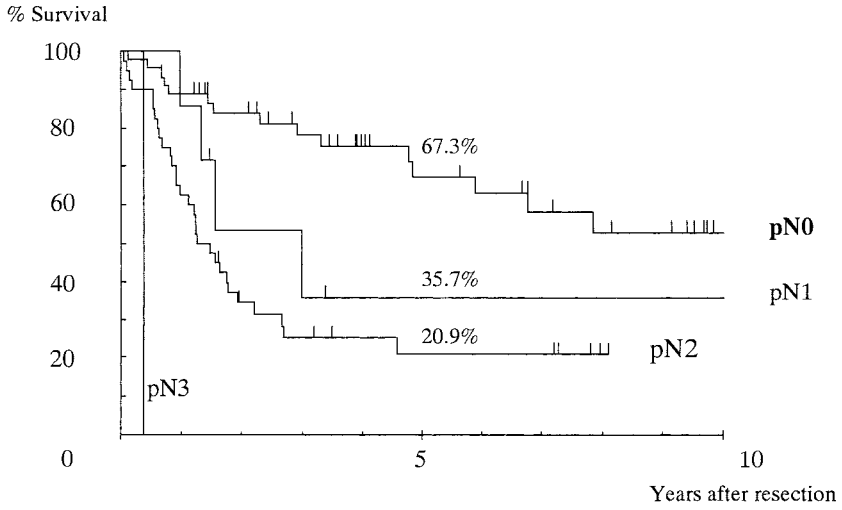

Fig. 1. Survival curves of 94 patients with clinical N2 (cN2) stage non-small cell lung cancer. pN0, patients diagnosed clinically with cN2 disease but who actually had pathologic N0 (pN0) disease (n=45); pN1, clinical diagnosis of cN2 disease but actually was pN1 disease (n=8); pN2, clinical diagnosis of cN2 disease but actually was pN2 disease (n=40); pN3, clinical diagnosis of cN2 disease but actually was pN3 disease (n=1).

University Hospital. The 45 patients with pN0 disease confirmed by pathology comprised this study group. Prior to March 1997, patients with cN2 disease, except for those with bulky cN2 disease, who otherwise had operable lesions were considered surgical candidates. There were 36 men and 9 women, with a mean age of 65-years (range, 45 to 81 years).

Diagnostic evaluation and surgical technique

All patients were staged clinically according to the TNM classification system of the International Union Against Cancer (UICC).[3] Stage was determined based on chest roentgenography, bronchoscopy, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging (MRI) or CT of the brain, and bone scan. Sputum cytology and/or bronchoscopic biopsy or cytology were done to confirm malignancy and establish the histologic type of tumor. Mediastinal lymph node (MLN) involvement was determined by staff radiologists based on CT findings. MLNs with a short-axis diameter greater than 1 cm, 1.5 cm for the subcarinal nodes, were considered positive. Bulky cN2 disease was defined as two or more MLNs larger than 2 cm. Mediastinoscopy was not performed except when contralateral nodal involvement was suspected. In all cases, the extent of resection was at least a lobectomy, and was combined with systematic mediastinal lymphadenectomy. Histology was determined according to the World Health Organization Classification system.

Comparison of subgroups

The hospital records of the 45 patients with cN2-pN0 disease were retrospectively reviewed. We retrieved information about the following factors which were available pre- or intraoperatively: (a) clinical characteristics (age, gender, serum carcinoembryonic antigen [CEA] concentration, extent of the resection [lobectomy or bilobectomy vs. pneumonectomy]), (b) characteristics of the primary tumor (side [right vs. left], lobar distribution [upper lobe vs. lower lobe vs. main bronchus], size [≤3 cm vs. >3 cm], invasion of visceral pleura [absent vs. present], invasion of parietal pleura [absent vs. present], more than one discrete tumor nodule in the same lobe [absent vs. present], histology [squamous cell carcinoma vs. non-squamous cell carcinoma]).

Statistical analysis

Survival was calculated by the Kaplan-Meier method. Log-rank statistics were used for univariate analysis, and the data were considered significant when the p-value did not exceed 0.05. Cox proportional hazards model was performed with a conditional backward procedure. All the prognostic factors were used as covariates. The data were considered significant when the p value was <0.05.

Results

Overall survival

The overall 5-year survival rate for patients with resected cN2 disease was 43.4% (n=94). Postoperative survival of cN2 patients classified by the pN-stage is shown in Fig. 1. The 5-year survival rate was 67.3% for cN2-pN0 disease (n=45), 35.7% for cN2-pN1 disease (n=8), 20.9% for cN2-pN2 disease (n=40), and 0% for cN2-pN3 disease (n=1).

Table 1. Five-year survival rates in patients with cN2-pN0 non-small cell lung cancer who have negative prognostic factors

Variable	No. of patients	5-year survival rate (%)	p value
Total group	45	67.3	–
Age			0.56
<60 years	14	78.6	
≥60 years	31	61.7	
Gender			0.79
Men	36	63.7	
Women	9	80.0	
CEA (ng/mL)[a]			0.02
<2.5	24	81.0	
≥2.5	19	36.9	
Tumor side			0.88
Right	26	70.9	
Left	19	63.3	
Lobar distribution			0.47
Upper lobe	28	68.2	
Lower lobe	15	67.0	
Main bronchus	2	50.0	
Tumor size[a]			0.49
≤3 cm	12	62.5	
>3 cm	31	70.8	
Invasion of visceral pleura			0.05
Absent	36	71.5	
Present	9	51.9	
Invasion of parietal pleura			0.24
Absent	40	69.9	
Present	5	0.0	
Multiple discrete tumor nodules in the same lobe			0.65
Absent	43	67.9	
Present	2	50.0	
Tumor histology			0.71
Squamous cell carcinoma	24	64.8	
Non-squamous cell carcinoma	21	70.9	
Extent of resection			0.01
Lobectomy or bilobectomy	40	75.1	
Pneumonectomy	5	20.0	

CEA, carcinoembryonic antigen.
[a]The sum of the subgroups does not equal 45 because of missing data.

cN2-pN0 disease

A number of factors have been analyzed to assess their effect on survival after resection of cN2-pN0 disease (Table 1). Patients with a CEA concentration <2.5 ng/mL had better survival (5-year survival, 81.0%) than patients with a CEA concentration ≥2.5 ng/mL (36.9%, p=0.02). The extent of primary tumor also was an important prognostic factor. Patients without invasion of the visceral pleura had a 5-year survival of 71.5%; 5-year survival was 51.9% when invasion of the visceral pleura was present (p=0.05). The survival was better in patients who underwent lobectomy or bilobectomy (5-year survival, 75.1%) than in those who underwent pneumonectomy (20.0%, p=0.01). There were no significant differences based on age, gender, tumor side, lobar distribution, tumor size, invasion of parietal pleura, multiple discrete tumor nodules in the same lobe, and tumor histology (Table 1).

Invasion of the visceral pleura had a negative impact on survival (p=0.01), as did the preoperative CEA concentration (p=0.03) (Table 2). The extent of resection was not a prognostic factor according to the Cox model. When these two negative prognostic factors, visceral pleural invasion and a high CEA concentration were combined, we found obvious survival differences among patients with cN2-pN0 disease (Fig. 2). The 5-year survival of

Table 2. Covariates related to survival in the Cox model in patients with cN2-pN0 disease[a]

Variable	Hazard ratio	95% CI	p value
Invasion of visceral pleura			
Present vs. absent	3.97	1.35-11.66	0.01
CEA (ng/mL)			
≥2.5 vs. <2.5	3.61	1.16-11.32	0.03

CEA, carcinoembryonic antigen; CI, confidence interval.
[a]The sum of the group does not equal 45 because CEA concentration was unknown in two cases.

patients with both negative factors (n=6) was 0%, while that of patients who had neither factor (n=21) was 78.1% (p<0.01) and that of patients who had only one was 63.0% (n=16) (p<0.01).

Discussion

Surgical extirpation is the only potentially curative treatment for NSCLC. The 5-year survival rates in patients with pN0 disease vary from 38% (T3N0) to 67% (T1N0).[1)] These figures are unsatisfactory. Considering recent success using induction chemotherapy to treat early-stage NSCLC,[1,2)] prognostic factors that can be identical pre- or intraoperatively are needed for optimal treatment.

The presence of visceral pleural invasion and a high CEA concentration are negative prognostic factors in cN2-pN0 disease. Visceral pleural invasion has been reported as a negative prognostic factor previously.[4,5)] Ichinose et al.[4)] found that visceral pleural invasion was a negative prognostic factor in stage I (hazard ratio = 1.8463, 95% confidence interval [95% CI] = 1.1157-2.9495) and in stage II (hazard ratio = 2.0107, 95% CI = 1.0470-3.8613). The elevated serum CEA concentration is a well established negative prognostic factor.[6,7)]

There is a subgroup of patients who have poor prognosis with surgery alone. For patients with cN2-pN0 disease, who have both of these negative prognostic factors, the risk of death is 14.33 (3.97×3.61) times greater than for the overall group with cN2-pN0 disease who undergo resection (Table 2). Although cN2-pN0 disease is best treated by surgery, the addition of induction chemotherapy may improve the prognosis of this subgroup of patients, as it has for patients with stage IIIA N2 disease.[8,9)]

Our previous report, which analyzed prognostic factors in 40 patients who underwent resection of cN2-pN2 disease, found that absence of parietal pleural invasion, a low CEA concentration, and a single metastatic MLN station correlated with improved survival. Taken together with the present findings, pleural invasion, elevated CEA concentration and MLN involvement appear to be important negative prognostic factors in cN2 disease.

Thoracoscopy permits both T-staging and N-staging with little morbidity.[10,11)] Since April 1997, we have used thoracoscopy to stage every potential surgical candidate

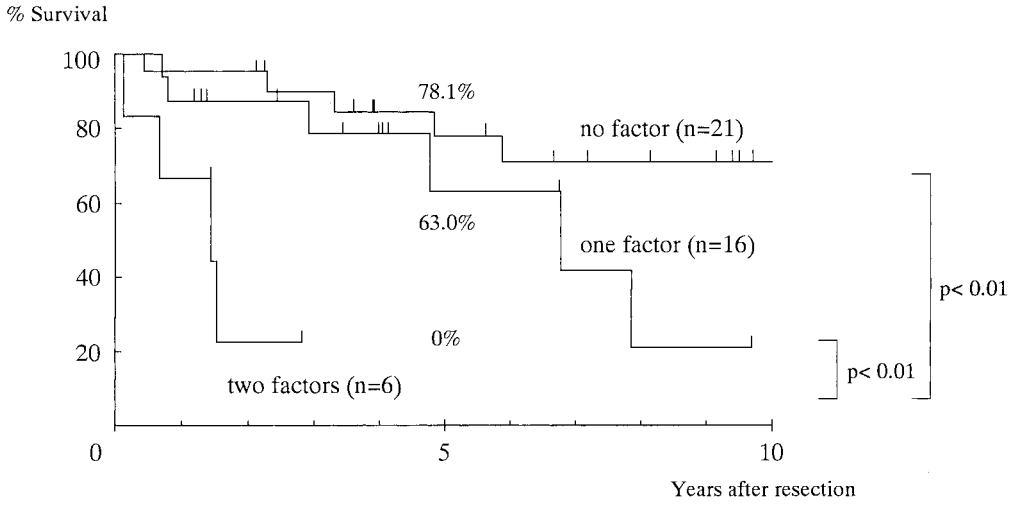

Fig. 2. Survival curves of patients with cN2-pN0 non-small cell lung cancer who did or did not have major negative prognostic factors: parietal pleural invasion and a CEA concentration ≥2.5 ng/mL. Survival curve of the subgroup with both negative factors (n=6) versus the subgroup with neither factor (n=21) or one factor (n=16) were different (p<0.01, respectively; log-rank test).

who was able to tolerate one-lung ventilation. Thoracoscopy allowed us to detect any pleural involvement and determine the extent of the primary tumor; a biopsy could be performed if necessary to confirm tumor invasion, and suspicious MLN lesions could be sampled.

Individualization of treatment in patients with cN2 NSCLC requires knowledge of whether the tumor has spread to the pleura, whether the CEA concentration is elevated, and whether the MLNs are involved. The presence of these negative prognostic factors suggests that surgery alone is unlikely to be curative in this patient cohort and that additional treatment is needed.

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