Clinicopathological Features in N0 Oesophageal Cancer Patients

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Abstract. *Background: The prognosis for patients with N0 oesophageal cancer is favourable, but relevant prognostic factors and appropriate surveillance protocols have not been identified for these patients. Patients and Methods: A total of 210 oesophageal cancer patients were included in this study. Of these, 92 (43.8%) had no lymph node metastasis. Predictive factors for lymph node metastasis were evaluated in N0 oesophageal cancer. Survival, prognostic factors, causes of death and pattern of recurrence were assessed between patients with and without lymph node metastasis. Results: Logistic regression analysis revealed that depth of tumour invasion (T1) was an independent predictive factor for N0. The Cox proportional hazard regression model showed that venous invasion was an independent prognostic factor for disease-specific survival in N0 oesophageal cancer patients (hazard ratio=3.977, p=0.042). Locoregional recurrence was less frequent in patients with N0 oesophageal cancer (p=0.0319). Conclusion: Meticulous and long-term follow-up is necessary even for patients with N0 oesophageal cancer, parti-cularly for those with adverse prognostic factors.*

Lymph node metastasis is one of the most important prognostic factors in patients with oesophageal cancer (1, 2). Abundant and complicated lymph–capillary networks develop in the lamina propria mucosae and the submucosa throughout the oesophagus, so that lymph node metastasis spreads widely in the early phases of oesophageal tumour progression (3, 4).

It is therefore important to perform an appropriate lymph node dissection according to tumour stage. Preoperative diagnosis of lymph node metastasis in patients with oesophageal cancer is difficult. Therefore, two-field lymph node dissection has been commonly performed in patients with middle or lower thoracic oesophageal cancer, and three-field lymph node dissection in those patients with middle or upper thoracic oesophageal cancer for tumours deeper than submucosa in some institutes in Japan (5).

Although surgical outcomes in patients without lymph node metastasis are fairly satisfactory, locoregional recurrence and distant metastasis can still develop (6). A retrospective study evaluating clinicopathological characteristics and prognostic factors of N0 oesophageal cancer is important in order to be able to design an appropriate therapeutic strategy for such patients. It may be beneficial if the indication of adjuvant chemotherapy and less extensive surgery is clear or the follow-up system is simplified in N0 oesophageal cancer. To this end, this study compared clinicopathological characteristics, surgical outcomes, prognostic factors and patterns of recurrence between oesophageal cancer patients with and without lymph node metastasis.

Patients and Methods

Patients. Between April 1992 and March 2005, a series of 268 patients with thoracic oesophageal squamous cell carcinoma underwent transthoracic oesophagectomy. Of these, 210 patients underwent curative oesophagectomy classified as R0 (with no residual tumour) and two-field or three-field lymph-node dissection in the Department of Surgery Gastroenterological Center and the Department of Gastroenterological Surgery, Yokohama City University, Japan. Data were retrieved from operative and pathological reports, with follow-up data being obtained from the outpatient clinical database.

All subjects were preoperatively confirmed to have oesophageal squamous cell carcinoma by analysis of endoscopic biopsy specimens. Of the 210 patients receiving R0 resection (174 men and 36 women, age range, 30-81 years, mean age±standard deviation [SD], 62.9±8.1 years), 118 had lymph node metastasis while 92 did not.

Preoperative evaluation. A preoperative evaluation was performed for all patients, and consisted of a barium-swallow study, an endoscopic examination with a biopsy, and computed tomography (CT) scans. The tumour diameter and depth of invasion were measured by both endoscopic examination and a barium-swallow

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study. Lymph-node metastasis, depth of invasion, and staging were principally based on the International Union Against Cancer UICC/TNM classification (7). Experienced pathologists at each institution participated in the study, and ensured the quality of the pathological diagnoses.

Of the 210 registered patients, 90 had tumours located in the lower thoracic oesophagus, 105 in the middle thoracic oesophagus, and 15 in the upper thoracic oesophagus. Superficial type tumours (flat or elevated, depressed, and mixed type [elevated plus depressed]) were seen in 60 patients, well-defined type tumours in 79 and ill-defined type tumours were seen in the remaining 61 patients.

The pathologic tumour diameter corresponded to the maximum microscopic length of the tumours, irrespective of the depth. Patients were classified into two groups (<50 mm *versus* ≥50 mm) based on the pathologic tumour diameter: tumours measuring <50 mm were observed in 118 patients, and tumours measuring ≥50 mm were observed in the remaining 92 patients.

Histologically, T1 was observed in 69 patients, T2 in 50 patients, and T3/4 in 91 patients. Well-differentiated squamous cell carcinoma was observed in 53 patients, moderately differentiated squamous cell carcinoma in 102 and poorly differentiated squamous cell carcinoma in 55. Among the registered patients, 50 were classified as stage I, 36 as stage IIA, 57 as stage IIB and 67 as stage III.

Definition of recurrence. Locoregional recurrence was defined as tumours occurring at lymph nodes in the neck, mediastinum including anastomotic site, or upper abdomen at the site of initial oesophagectomy and lymph node dissection. Distant recurrence was defined as haematogenous within the solid organ, lymph node at the abdominal para-aorta, or peritoneal metastasis. Diagnosis of recurrence was made histologically, cytologically and radiologically. Combined recurrence was defined as the simultaneous detection of both loco-regional and distant recurrence within 30 days.

Surgical procedures. Two-field oesophagectomy (complete dissection of the mediastinal and abdominal regional lymph nodes) was performed in 164 patients. Three-field oesophagectomy (complete dissection of the mediastinal, abdominal and cervical regional lymph nodes) was performed in 46 patients. Principally, two-field oesophagectomy was employed in patients with tumours in the middle or lower thoracic oesophagus, and three-field oesophagectomy in patients with tumours in the upper thoracic oesophagus irrespective of metastatic lymph nodes, or the middle thoracic oesophagus with metastatic lymph nodes in the neck.

Surgery was performed after all possible alternative procedures or treatments had been explained to the patients, and they had given their informed consent.

Neoadjuvant and adjuvant treatments. Neoadjuvant or adjuvant treatments were not employed, as therapeutic outcomes were expected to be fairly satisfactory in patients without lymph node metastasis. Adjuvant chemotherapy was performed in patients with pathologically identified lymph node metastasis and good performance status, and who had given their informed consent: 600 mg/m^2 5-fluorouracil and 6 mg/m^2 cisplatin were intravenously administered for two weeks at 2-day intervals. The protocol was continued twice a year for two years.

Follow-up protocol. All patients underwent a blood examination every three months, a CT scan every six months, and an annual endoscopic examination. If gastrointestinal symptoms were reported, an additional examination was carried out. After the fifth year, patients received an annual check-up at an outpatient clinic.

The mean follow-up time was 51.1±47.2 months. There was no significant difference in follow-up time between patients with and without lymph node metastasis (47.8±45.4 months *versus* 54.9±48.7 months).

Statistical analysis. SPSS version 10.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. The Chi-square test or the Fisher exact test was applied to evaluate the differences in proportions, and the Student's *t*-test was used to evaluate the continuous variables. The predictive factors for lymph node metastasis were evaluated by univariate analysis using the following seven variables: age, gender, tumour location, tumour diameter, macroscopic appearance, depth of invasion and histological type. The logistic regression model was used to assess independent predictive factors of lymph node metastasis using the variables deemed to be significant by univariate analysis.

For the N0 oesophageal cancer patients, survival curves according to the following 10 variables were constructed using the Kaplan-Meier method and compared using the log-rank test: age, gender, tumour location, tumour diameter, macroscopic appearance, depth of invasion, histological type, lymphatic invasion, venous invasion and lymph node dissection. Cox proportional regression analysis for disease-specific survival was applied using the variables deemed to be significant by univariate analysis. For the patients with lymph node metastasis, the number of lymph node metastases was added in these analyses. A probability value of $p<0.05$ was considered statistically significant.

The Institutional Review Board at the host institute approved this retrospective study.

Results

Comparison of clinicopathological characteristics between patients with and without lymph node metastasis. In patients without lymph node metastasis, macroscopically superficial-type tumours were significantly more common, tumour invasion was significantly more superficial, and the number of dissected lymph nodes was significantly fewer than in patients with lymph node metastasis. There were no signifi-cant differences in any other variable between the two groups (Table I).

Predictive factors for lymph node metastasis. Logistic regression analysis showed that depth of invasion was an independent predictive factor for lymph node metastasis ($\chi^2=32.08$, $p<0.001$). The odds ratio (95% confidence interval) for T2 tumours was 8.333 (3.609-19.241), and that for T3/4 tumours was 5.352 (2.696-10.621) compared to T1 tumours. As a result, T1 tumour was an independent predictive factor for N0 oesophageal cancer.

Survival time. The rate of overall 5-year survival was 75.5% in patients without lymph node metastasis and 38.8% in patients with lymph node metastasis, which was statistically significant ($p<0.0001$) (Figure 1). The rate of disease-

Table I. *Clinicopathological characteristics of patients with and without lymph node metastasis.*

Variable	*p*N(–) (n=92)	*p*N(+) (n=118)	*p*-Ωalue
Age (years)			0.135
<75	84	114	
≥75	8	4	
Sex			0.713
Male	75	99	
Female	17	19	
Tumour location			0.226
Lower thoracic	44	46	
Middle thoracic	44	61	
Upper thoracic	4	11	
Tumour diameter (mm)			0.401
<50	55	63	
≥50	37	55	
Macroscopic appearance			<0.001
Superficial	42	18	
Well-defined	25	54	
Ill-defined	15	46	
Depth of invasion			<0.001
T1 (mucosa,submucosa)	50	19	
T2 (muscularis propria)	12	38	
T3, 4 (adventitia, adjacnet organs)	30	61	
Histological type			0.142
Well diff. squamous	29	24	
Moderately diff. squamous	43	59	
Poorly diff. squamous	20	35	
Lymph node dissection			0.019
Two-field	79	85	
Three-field	13	33	
Number of dissected lymph nodes	32.3±17.2	38.7±16.6	0.001

*p*N(+): Patients with lymph node metastasis, *p*N(–): patients without lymph node metastasis.

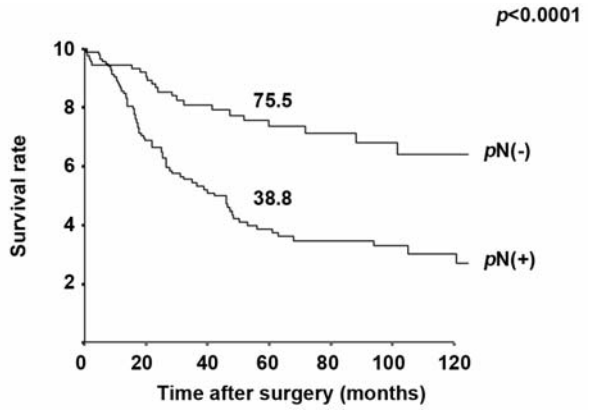

Figure 1. *Overall survival in patients with and without lymph node metastasis. The rate of overall 5-year survival was 38.8% in patients with, and 75.5% in patients without lymph node metastasis. This difference was statistically significant between the two groups (p<0.0001). pN(+): Patients with lymph node metastasis, pN(–): patients without lymph node metastasis.*

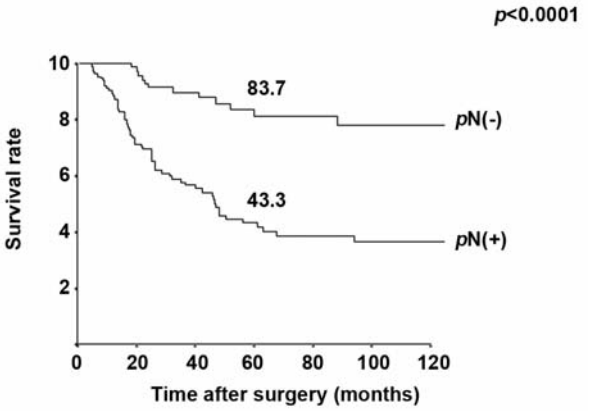

Figure 2. *Disease-specific survival in patients with and without lymph node metastasis. The rate of disease-specific survival was 43.3% in patients with, and 83.7% in patients without lymph node metastasis. This difference was statistically significant between the two groups (p<0.0001). pN(+): Patients with lymph node metastasis; pN(–): patients without lymph node metastasis.*

specific survival was also statistically significantly different between the two groups (p<0.0001), at 83.7% in patients without lymph node metastasis and 43.3% in patients with lymph node metastasis (Figure 2).

Prognostic factors by univariate analysis. Univariate analysis showed that macroscopically well-defined tumours, deeper tumours and tumours having venous invasion were asso-ciated with significantly worse prognosis in patients without lymph node metastasis. By contrast, larger tumours, deeper tumours, tumours having lymphatic invasion and tumours with many metastatic lymph nodes significantly influenced adverse prognosis in patients with lymph node metastasis (Table II).

Prognostic factors by the Cox proportional hazard regression model. Multivariate analysis revealed that venous invasion was an independent prognostic factor in patients without lymph node metastasis. By contrast, the analysis showed that the presence of more than four metastatic lymph nodes and lymphatic invasion independently influenced adverse prognosis in patients with lymph node metastasis (Table III).

Tumour recurrence. Recurrence was observed in 11 patients without lymph node metastasis (12.0%) and 56 patients with lymph node metastasis (47.5%), which was a statistically significant difference (p<0.0001). There was also a significant difference in the distribution of each recurrent pattern with and without lymph node metastasis (p=0.0319) (Table IV). In patients without lymph node metastasis, loco-regional recurrence was less frequent.

Table II. *Prognostic factors in patients with and without lymph node metastasis.*

Variables	Lymph node metastasis (–)			Lymph node metastasis (+)		
	n	5-Year survival rate (%)	*p*-Value	n	5-Year survival rate (%)	*p*-Value
Age (years)			0.4996			0.1172
<75	84	80.7		114	46.1	
≥75	8	-		4	-	
Sex			0.6526			0.5754
Male	75	82.0		99	44.6	
Female	17	77.3		19	45.6	
Tumour location			0.4418			0.5617
Lower thoracic	40	87.1		46	40.9	
Middle thoracic	44	73.2		61	48.3	
Upper thoracic	4	-		11	40.0	
Tumour diameter (mm)			0.7827			0.0381
<50	55	80.2		63	58.3	
≥50	37	81.7		55	29.7	
Macroscopic appearance			0.0292			0.3782
Surperficial	42	92.1		18	70.5	
Well-defined	25	61.1		54	45.8	
Ill-defined	25	87.1		46	37.8	
Depth of invasion			0.0389			0.0216
T1 (mucosa, submucosa)	50	93.1		19	80.4	
T2 (muscularis propria)	12	57.1		38	43.5	
T3, 4 (adventitial, adjacent organs)	30	73.2		61	31.2	
Histological type			0.3559			0.2184
Well diff. squamous	29	80.1		24	37.8	
Moderately diff. squamoue	43	89.1		59	51.2	
Poorly diff. squamous	20	70.7		35	38.3	
Lymphatic invasion			0.8414			0.0110
Absence	73	81.5		30	68.5	
Presence	19	77.4		88	36.7	
Venous invasion			0.0276			0.0459
Absence	57	91.7		45	55.1	
Presence	35	67.2		73	37.6	
Lymph node dissection			0.8385			0.9782
Two-field	79	82.7		85	42.3	
Three-field	13	77.1		33	48.2	
Metastatic lymph nodes						0.0011
≤3	-			86	53.2	
≥4	-			32	22.9	

Lymph node recurrence was observed in 10 patients (one locoregional, one distant and eight combined). Of these, five patients had regional lymph node recurrence and five had non-regional lymph node recurrence. Of the five patients with regional lymph node recurrence, two recurrences were observed in the left nerve lymph node, two in the left retromediastinal lymph node and one in the left tracheo-bronchial lymph node.

Cause of death. Cause of death according to the time after surgery was evaluated in each group. There was a significant difference in the number of patients who died of oesophageal cancer between patients with and without lymph node metastasis (56/32 *versus* 11/81, $p<0.001$). However, there was no significant difference in the number of patients who died of co-morbid disease or other malignant disease between patients with and without lymph node metastasis (11/107 *versus* 11/81, $p=0.6508$). The distribution of time of death after surgery did not differ in patients with and without lymph node metastasis in those who died of oesophageal cancer ($p=0.7714$), and in those who died of co-morbid disease or other malignant diseases ($p=0.7765$) (Table V).

Timing and pattern of recurrence. The distribution of timing of death did not differ between patients with and without lymph node metastasis according to the pattern of recurrence (Table VI).

Table III. *Independent prognostic factors for disease-specific survival.*

Variables	χ^2	Odds ratio (95% CI)	*p*-Value
I: *p*N(–)			
Venous invasion	4.155		0.042
Absence		1	
Presence		3.977 (1.055-14.999)	
II: *p*N(+)			
Number of metastatic lymph nodes	8.420		0.004
≤3		1	
≥4		2.215 (1.294-3.789)	
Lymphatic invasion	4.939		0.026
Absence		1	
Presence		2.348 (1.106-4.984)	

*p*N(+): Patients with lymph node metastasis, *p*N(–): patients without lymph node metastasis, 95% CI: 95% confidence interval.

Discussion

In the present study, the depth of tumour invasion was shown to be a predictive factor for lymph node metastasis in patients with oesophageal cancer. Conversely, lymph node metastasis was less frequent in patients with T1 oesophageal cancer. In patients without lymph node metastasis, venous invasion was an independent prognostic factor, while in patients with lymph node metastasis the number of metastatic lymph nodes, tumour diameter and lymphatic invasion were independent prognostic factors. Locoregional recurrence was less frequent in patients without lymph node metastasis.

In oesophageal cancer, the incidence of lymph node metastasis is relatively high due to the abundant lymphatic plexus in the oesophageal wall (8, 9). Even in submucosal tumours, the incidence of lymph node metastasis is approximately 50% (10), suggesting implications for surgical treatment.

Lymph node metastasis was the most important prognostic factor in patients with oesophageal cancer as shown in the present study. Lymph node metastasis is defined according to the anatomical distribution and the number of metastatic lymph nodes in the Japanese classification of oesophageal carcinoma (11). By contrast, in the UICC/TNM classification 7th edition, its definition is based only on the number of lymph node metastases (7). The number of metastatic lymph nodes (≤3 *versus* ≥4) was also found to be an independent prognostic factor in a previous study of patients with oesophageal cancer (12). Moreover, the ratio of metastatic lymph nodes was an important prognostic factor for survival in these patients (13).

In Japan, transthoracic en bloc oesophagectomy is regularly and routinely performed. Three-field lymph node dissection is common for upper thoracic oesophageal cancer tumours and two-field lymph node dissection is prevalent for middle or lower thoracic oesophageal cancer tumours. This treatment can provide satisfactory surgical outcomes (5, 14). In a randomised Dutch trial, extended lymph node dissection for oesophageal cancer achieved better survival rates than limited lymph node dissection (15). Another study found that the total number of retrieved lymph nodes could be used to predict survival in oesophageal cancer and suggested that at least 18 lymph nodes should be retrieved (16). Similar results were obtained in patients without lymph node metastasis (17). Therefore, a sufficient number of retrieved lymph nodes may be required to obtain satisfactory surgical outcomes even in patients with N0 oesophageal cancer.

Table IV. *Pattern of recurrence in patients with and without lymph node metastasis. Probability p-value between the two groups: p=0.0319.*

Variables	*p*N(–) (n=92)	*p*N(+) (n=118)
Locoregional	1	24
Distant	2	14
Combined	8	18

*p*N(+): Patients with lymph node metastasis, *p*N(–): patients without lymph node metastasis.

In a report focusing on prognostic factors in N0 oeso-phageal cancer (6), T-stage, adenocarcinoma and degree of differentiation independently influenced adverse outcomes. Contrary to the present findings, venous invasion and tumour diameter had no prognostic value in that study. These differences may be due to the number of patients involved, perioperative treatments, and chemotherapy. It is necessary to confirm the validity of the present findings in a large cohort size.

It has been reported that the prevalence of immunohisto-chemically detected micrometastasis was 25-34% in pN0 oesophageal cancer (18, 19). Micrometastasis affected the

Table V. *Cause of death*.

	Oesophageal cancer		Co-morbid disease or other malignant disease	
	*p*N(–) (n=11)%	*p*N(+) (n=56)%	*p*N(–) (n=11)%	*p*N(+) (n=11)%
Time after surgery (months)				
<12	0 (0)	10 (17.9)	5 (45.4)	3 (27.3)
12 to 24	5 (45.4)	22 (39.3)	1 (9.1)	1 (9.1)
24 to 36	2 (18.2)	10 (17.9)	2 (18.2)	2 (18.2)
36 to 48	2 (18.2)	7 (12.5)	0 (0)	1 (9.1)
48 to 60	1 (9.1)	4 (7.1)	0 (0)	1 (9.1)
≥60	1 (9.1)	3 (5.4)	3 (27.3)	3 (27.3)

*p*N(+): Patients with lymph node metastasis, *p*N(–): patients without lymph node metastasis.

Table VI. *Timing and pattern of recurrence*.

	Locoregional		Distant		Combined	
	*p*N(–) (n=1)	*p*N(+) (n=24)	*p*N(–) (n=2)	*p*N(+) (n=14)	*p*N(–) (n=8)	*p*N(+) (n=18)
Time after surgery (months)						
<12	0	6	0	1	0	3
12 to 24	0	7	1	8	4	7
24 to 36	0	2	1	3	1	5
36 to 48	0	5	0	1	2	1
48 to 60	0	2	0	1	1	1
≥60	1	2	0	0	0	1

*p*N(+): Patients with lymph node metastasis, *p*N(–): patients without lymph node metastasis.

prognosis for N0 oesophageal cancer and was associated with a high incidence of both locoregional and distant recurrence in these studies. Conclusive evidence suggested that lymph node micrometastasis should be included in the staging system.

In the present study, lymph node recurrence was observed in 10 patients, although its incidence was significantly lower than in patients with lymph node metastasis. These 10 patients may have had lymph node micrometastasis at the initial operation. Five of these patients had regional lymph node recurrence at the left side of the mediastinum. Technical difficulties involved in complete dissection of the lymph nodes may have resulted in lymph node recurrence, even in regional lymph nodes. Indeed, half of the lymph node recurrences in this study were detected in non-regional lymph nodes. In these patients, sentinel lymph nodes were present outside the regional area and all patients had combined recurrence. Clinically, it may be meaningless to detect sentinel lymph nodes outside the regional area and to dissect them fully in all patients. It may therefore be necessary to administer adjuvant chemotherapy to prevent recurrence even in patients with N0 oesophageal cancer patients with venous invasion, which is an independent prognostic factor.

A study demonstrated that the major cause of death in N0 oesophageal cancer is a second malignancy (20). It was concluded that new strategies aimed at preventing or treating synchronous and subsequent malignancies could prolong the survival of these patients (20). However, in the present study, there was no significant difference in the incidence of co-morbid disease or other malignant disease between patients with and without lymph node metastasis. This difference between the present study and that of Sato *et al*. (20) may have been due to differences in the follow-up system of the two studies.

In the present study, the timing of death according to cause did not differ between patients with and without lymph node metastasis. Moreover, there was no correlation between the timing and pattern of recurrence between the two groups. Therefore, meticulous long-term follow-ups are necessary for oesophageal cancer patients either with or without lymph node metastasis in order to achieve early detection.

NCCN oesophageal cancer guidelines of 2010 do not recommend adjuvant chemotherapy after R0 resection in squamous cell oesophageal cancer patients without lymph node metastasis (21). However, a previous study found that

adjuvant chemotherapy produced a therapeutic effect in patients with N1 oesophageal cancer (22), so a future randomised controlled trial of adjuvant chemotherapy in a larger volume of N0 oesophageal cancer patients with venous invasion would be useful.

In conclusion, the present study identified venous invasion as an adverse prognostic factor in N0 oesophageal cancer. Meticulous and long-term follow-up was shown to be necessary, particularly for those patients with adverse prognostic factors, as well as for patients with lymph node metastasis.

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