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Clinicopathologic characteristics and survival of patients with clinical Stage I squamous cell carcinomas of the thoracic esophagus treated with three-field lymph node dissection

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Abstract

Objective: Clinicopathologic characteristics and survival rates of patients with clinical Stage I tumors treated with three-field lymph node dissection have not been well investigated. This report documents the results of a series of cases of clinical Stage I squamous cell carcinomas treated with this surgical procedure in our institute. **Methods:** From January 1988 to March 1997, 326 patients with carcinomas of the thoracic esophagus underwent transthoracic esophagectomy with three-field lymph node dissection. Two hundred and ninety-seven (91%) of these had squamous cell carcinomas. Fifty-seven (18%) patients with clinical Stage I squamous cell carcinomas of the thoracic esophagus were retrospectively reviewed here. **Results:** Among 57 clinical Stage I squamous cell carcinomas, ten (18%) were diagnosed as T1-mucosal and 47 (83%) as T1-submucosal. Seventy percent of the patients with clinical T1-mucosal tumors had additional primary esophageal lesions. The operative morbidity and in-hospital mortality rates were 63 and 0%, and the overall 1-, 3-, 5-, and 10-year survival rates were 95, 86, 78, and 70%, respectively. Of the 57 tumors assessed pathologically, 12 (21%) were T1-mucosal, 42 (74%) were T1-submucosal, and three (5%) were T2. Nineteen (33%) exhibited lymph node metastasis. The 1-, 3-, 5-, and 10-year survival rates for patients with lymph node metastasis were 90, 79, 73, and 58%, respectively, as compared with 97, 90, 80, and 76, respectively for patients without lymph node metastasis ($P = 0.24$). The accuracy of preoperative staging, based on both wall penetration and the status regarding lymph node metastasis, was 63%. With reference to the 1997 UICC-TNM staging system, 36 (63%) were pStage I, two (4%) were pStage IIA, 18 (28%) were pStage IIB, and three (6%) were pStage IVB. The 1-, 3-, 5-, and 10-year survival rates for patients with pStage I disease were 97, 92, 85, and 81%, respectively. In those with pStage II or IV disease, the values were 91, 76, 65, and 52%, respectively. **Conclusions:** Three-field lymph node dissection may be indicated even for patients with clinical Stage I squamous cell carcinoma requiring surgical intervention because this surgical procedure provides for possible cure by removing unsuspected lymph node metastasis. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Esophageal carcinoma; Squamous cell carcinoma; Three-field lymph node dissection; Clinical Stage I; Lymph node metastasis

1. Introduction

Owing to improvements in preoperative diagnostic measures, the likelihood of encountering early stage carcinoma of the thoracic esophagus has increased [1–3]. Clinical evaluation of tumor invasion and the absence or presence of nodal involvement is important for deciding which therapeutic procedures are most appropriate. Clinical Stage I disease, defined as a T1 (mucosal or submucosal) tumor lacking lymph node and distant organ involvement according to the 1997 UICC-TNM classification [4], corresponds to early

phase carcinoma of the esophagus. Therefore, control of the local tumor has been considered sufficient for treatment [5–7]. However, endoscopic mucosal resection cannot provide any information of nodal involvement. Moreover, non-invasive treatment modalities such as laser therapy, radiation therapy, chemoradiation therapy, and photodynamic therapy, cannot assess either the tumor extension or the status of lymph node metastasis pathologically.

Clinicopathologic characteristics and survival rates for patients with clinical Stage I tumors undergoing extensive lymph node dissection have not been well investigated. This report represents results of three-field lymph node dissection for a series of cases of clinical Stage I squamous cell carcinoma of the esophagus.

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2. Patients and methods

2.1. Patients

From January 1988 to March 1997, 326 patients with carcinomas of the thoracic esophagus underwent transthoracic esophagectomy with three-field lymph node dissection at the National Cancer Center Hospital, Tokyo. Among them, 297 (91%) patients had squamous cell carcinomas and 84 (26%) had clinical T1 tumors. Fifty-seven (18%) had clinical Stage I squamous cell carcinomas of the thoracic esophagus. Their records were retrospectively reviewed here. The ages of the 54 males and three females ranged from 46 to 86 years, with a mean of 62 years.

Preoperative evaluation was performed for all patients with barium swallow examination, endoscopy with biopsy, computed tomography (CT) scans from the neck to the abdomen, and ultrasonography of the neck and upper abdominal compartment. Endoscopic ultrasonography (EUS) was performed for 50 patients with an echoendoscope with either 7.5 or 20 MHz frequencies. Wall penetration of a tumor for clinical T categorization was based on the deepest invasion evident on barium swallow examination, endoscopy, or EUS. Lymph node or distant organ metastases were not evident in any of the patients on preoperative evaluation. Postoperative staging according to the 1997 UICC-TNM classification was based on pathologic examination of the resected specimens, including the dissected lymph nodes.

At last follow-up, March 2000, 41 patients were still alive without recurrence of disease. The median follow-up period for these 41 survivors was 79 months, with a range of 37–140 months. Three patients had died of recurrent cancer: one of mediastinal lymph node recurrence and two of distant organ metastases. Twelve died of causes other than recurrence of cancer: six of pneumonia, three of other cancers (two of synchronous stomach cancers and one of a synchronous cancer of the hypopharynx), two of heart failure, and one of a brain infarction. Information about the cause of death was not available for one patient.

2.2. Surgical procedures

All 57 patients underwent right thoracotomy. The bilateral recurrent laryngeal nerve nodes, upper periesophageal, right paratracheal, and infra-aortic arch nodes were dissected as the upper mediastinal lymph nodes. The middle mediastinal nodes comprised the subcarinal, bilateral bronchial, and middle periesophageal nodes, and the lower mediastinal nodes comprised the lower periesophageal, posterior mediastinal, and supradiaphragmatic nodes. All were removed.

Each patient was placed in a supine position after closure of the chest. The deep cervical lymph nodes comprising the internal jugular nodes below the level of the cricoid cartilage and the supraclavicular nodes, and the cervical paratracheal nodes were resected bilaterally via collar skin

incision in the neck. The abdominal lymph nodes, comprising the bilateral paracardiac nodes, the perigastric lesser curvature nodes, the left gastric nodes, the common hepatic artery nodes, the splenic artery nodes, and the celiac nodes were also removed.

Gastrointestinal continuity was restored with the stomach in 52 patients through a retrosternal route. Colon interposition was performed for five patients through a subcutaneous route, three with synchronous gastric carcinomas, and the remaining two having undergone a distal gastrectomy for peptic ulcer disease previously. Anastomoses of all patients were performed at the neck.

2.3. Statistical analysis

Survival was measured from the date of surgery until death or until the most recent follow-up investigation, March 2000. Survival curves were calculated according to the Kaplan–Meier method, including all causes of death, and log–rank statistics were used for comparisons. $P < 0.05$ was considered to be significant. Statistical calculations were conducted with Stat View 5.0J (Abacus Concepts Inc, Berkeley, CA, USA).

3. Results

3.1. Operative outcomes

The mean \pm SD duration of surgery was 476 ± 85 min and the operative blood loss was 584 ± 316 ml. Postoperative complications are listed in Table 1. The operative morbidity was 63%, 21 patients having an uncomplicated postoperative course. No patient died of postoperative complications within 30 days of surgery or during their hospital stay.

3.2. Clinicopathologic characteristics and survival rates

Clinicopathologic characteristics and survival rates are summarized in Table 2.

The tumor length of cT1-mucosal tumors, which means maximum longitudinal length measured on X-ray examination, ranged from 0.9 to 17.0 cm, with a mean of 2.1 cm, and

Table 1
Postoperative complications

Complication	<i>n</i> (%)
Anastomotic leak	18 (32)
Vocal cord palsy	11 (19)
Pneumonia	4 (7)
Wound infection	3 (5)
Empyema	1 (2)
Peritonitis	1 (2)
Cylothorax	1 (2)
Renal insufficiency	1 (2)
Anastomotic stricture	1 (2)
None	21 (37)

Table 2
Clinicopathologic characteristics of the 57 patients with clinical Stage I squamous cell carcinomas undergoing three-field lymph node dissection

Variable	No. of patients (%)	Overall survival rate (%)				P value (log-rank test)
		1-year	3-year	5-year	10-year	
Total		95	86	78	70	
T status						
cT1-mucosal	10 (18)	90	80	80	69	0.94
cT1-submucosal	47 (82)	96	87	77	70	
Tumor location						
Upper thoracic	9 (16)	78	78	78	78	0.94
Mid-thoracic	26 (46)	96	85	80	69	
Lower thoracic	22 (39)	100	91	74	66	
Multiple primary lesions						
Absent	39 (68)	95	87	78	71	0.81
Present	18 (32)	94	83	76	69	
Pathologic T status						
pT1-mucosal	12 (21)	92	83	83	83	0.01
pT1-submucosal	42 (74)	95	88	80	73	
pT2	3 (5)	100	67	33	0	
Lymph node metastasis						
Negative	38 (67)	97	90	80	76	0.24
Positive	19 (33)	90	79	73	58	
Pathologic N status						
pN0	40 (70)	98	90	81	77	0.14
pN1	17 (30)	88	77	70	55	
Pathologic M status						
pM0	54 (95)	94	87	78	70	0.54
pM1b	3 (5)	100	67	67	–	
Histological differentiation						
Well	10 (18)	80	80	69	41	0.03
Moderate	42 (74)	98	88	86	82	
Poor	5 (9)	100	80	40	–	
Lymphatic invasion						
Negative	32 (56)	97	88	80	71	0.88
Positive	25 (44)	92	84	75	69	
Vascular invasion						
Negative	47 (82)	98	87	80	70	0.57
Positive	10 (18)	80	80	69	69	
Pathologic stage						
Stage I	36 (63)	97	92	85	81	0.04
Stage II, IV	21 (37)	91	76	65	52	

that of cT1-submucosal tumors ranged from 0.8 to 22.0 cm, with a mean of 3.0 cm.

Among ten patients with cT1-mucosal tumors, seven (70%) had multiple primary lesions in the esophagus; six had two lesions and one had more than four lesions. Eleven (23%) of 47 with cT1-submucosal tumors had multiple primary lesions as follows: two lesions in six, three lesions in three, and more than four lesions in two patients. All the additional lesions were diagnosed by endoscopic examination with biopsy, and wall penetration was superficial (intraepithelial, mucosal, or submucosal) in all cases.

Pathologically, 12 were pT1-mucosal, 42 were pT1-

submucosal, and three were pT2 tumors. The relationship between clinical T status and pathologic T status is covered in Table 3. Approximately 95% (54/57) of clinical T1 tumors were predicted correctly as belonging to the T1 category. However, the accuracy for predicting wall penetration of T1-mucosal tumors was only 40% (4/10), whereas that for T1-submucosal tumors was 77% (36/47).

Nineteen (33%) had lymph node metastases, 17 (41%) among 42 patients with pT1-submucosal, and only one (8%) of 12 patients with pT1-mucosal tumors. There was one lymph node metastasis in nine patients, two lymph nodes with metastases in five, three nodes in three, and

Table 3

Relationship between clinical T and pathologic T status in patients with clinical Stage I squamous cell carcinomas

Clinical T status	Pathologic T status			Total
	pT1-mucosal	pT1-submucosal	pT2	
cT1-mucosal	4	6	0	10
cT1-submucosal	8	36	3	47
Total	12	42	3	57

four nodes in two. No patient had more than five nodes with metastases. Relationship between tumor location and anatomical sites of lymph node metastasis are given in Table 4. The most frequent lymph node metastasis occurred in the upper mediastinal nodes even with lower thoracic tumors. Among the total 57 patients, the incidence of cervical lymph node metastases was the same as that for middle or lower mediastinal lymph node metastases. Notably, seven (15%) out of the 48 patients with tumor in the mid- or lower thoracic esophagus, who were originally considered to be lymph node metastases negative, had become positive after three-field lymph node dissection.

Lymph node metastases were subdivided into N1 (regional node metastasis positive) and M1 (distant node metastasis positive) categories of the TNM staging system. Approximately 90% of patients with lymph node metastasis were classified as N1, and consequently classified into pStage IIB. Three patients were classified as having an M1b status (Stage IVB) because they had cervical lymph node metastases. Of these three, one died of distant organ metastasis at 23 months and the remaining two are still alive without recurrence of cancer at 39 and 68 months after surgery. Survival curves for patients with clinical Stage I tumors according to the pathologic stage are shown in Fig. 1. The 5- and 10-year survival rates of 16 patients with pathologic Stage IIB (pT1 N1 M0) disease were found to be 75 and 59%, respectively.

4. Discussion

There has been great controversy regarding surgical treatment, including extensive lymphadenectomy, for patients

Table 4

Relationship between anatomical location of tumors and lymph node metastasis for clinical Stage I squamous cell carcinoma cases undergoing three-field lymph node dissection

Anatomical location of lymph node metastasis	Tumor location of the thoracic esophagus			Total (% of 57)
	Upper (% of 9)	Mid (% of 26)	Lower (% of 22)	
Neck	0	2 (8)	1 (5)	3 (5)
Mediastinum	3 (33)	4 (15)	6 (27)	13 (23)
Upper	3 (33)	1 (4)	3 (14)	7 (12)
Middle	0	2 (8)	1 (5)	3 (5)
Lower	0	1 (4)	2 (9)	3 (5)
Abdomen	0	1 (4)	6 (27)	7 (12)

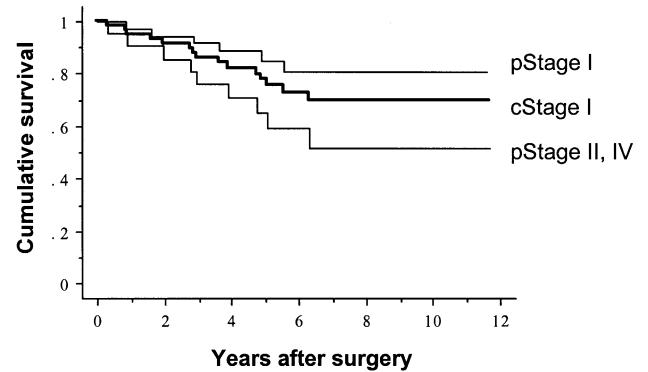


Fig. 1. Survival curves for patients with clinical Stage I tumors according to the pathologic stage with the 1997 UICC-TNM staging system.

with clinical Stage I carcinomas of the esophagus. Because clinical Stage I disease is defined as a T1 (mucosal or submucosal) tumor without either lymph node or distant organ metastases, local control would be normally sufficient for treatment. Therefore, various less invasive treatment modalities such as endoscopic mucosal resection, laser therapy, radiation therapy, chemoradiation therapy, brachytherapy, and photodynamic therapy have been indicated as therapeutic procedures.

However, it is well known that squamous cell carcinomas of the esophagus often develop as multiple primary lesions [8,9]. We previously reported that approximately 35% of patients with pathologic Tis or T1 tumors, so-called superficial carcinoma, had other primary lesions in the esophagus [9]. Furthermore, in the present series, 70% of patients with clinical T1-mucosal tumors had multiple primary carcinomas. These additional carcinomas of the esophagus make less invasive treatment modalities difficult to implement. Moreover, they do not allow assessment of wall penetration or the status regarding lymph node metastases pathologically. Because we consider extensive lymphadenectomy is indicated for patients judged able to tolerate surgical intervention even with apparently superficial carcinomas, we were able to clarify the true tumor extension, the presence and anatomical location of lymph node metastasis, and the accuracy of tumor staging.

Tumor penetration for clinical T categorization with the

1997 UICC-TNM staging system was assessed here by barium swallow examination, endoscopy, and EUS. CT scans could not depict the primary lesions as wall thickening of the esophagus. Nishimaki et al. reported that approximately 80% of pathologic T1 tumors could be given a clinical T1 categorization with each diagnostic measure [10]. In our series, the 95% accuracy obtained for predicting the tumor penetration of all T1 tumors was higher. However, for clinical T1-mucosal and T1-submucosal tumors the figures were 40 and 82%, respectively, and 60% of clinical T1-mucosal tumors were pathologically submucosal, a considerable underestimation.

Moghissi reported an approximately 70% overall and 80% disease-specific 5-year survivals of patients with clinical Stage I disease treated with two-field lymphadenectomy, despite using the 1983 classification of the American Joint Committee on Cancer [11]. All patients with clinical Stage I disease in that series were classified into pathologic Stage I because of no lymph node metastasis. In our series, 33% of the patients with clinically negative lymph node metastasis had positive nodes pathologically. Moreover, one of the highlights of our study was that 15% of the patients with tumors in the mid- or lower thoracic esophagus were found to have lymph node metastasis pathologically only after three-field lymph node dissection.

The absence or presence of lymph node metastasis is a major prognostic factor along with the depth of tumor invasion, and ultrasonography, CT scans, and EUS have been all assessed for determination of the nodal status [12–14]. Ultrasonography of the neck has an approximately 80% sensitivity and 95% accuracy for cervical lymph node metastasis, whereas, the accuracies of other diagnostic measures for predicting mediastinal or abdominal lymph node metastasis are at best 70%. The values for diagnostic measures in the present study were similar to those previously reported.

High incidences of lymph node metastasis among pathologic T1-submucosal tumors have been reported by authors from various institutes [1–3,15,16]. On the basis of these results, extensive lymphadenectomy including three-field lymph node dissection has been carried out for patients with clinical T1-submucosal or deeper tumors in Japan. The three-field approach maximizes the lymphadenectomy field, and the 5-year survivals of both patients with lymph node metastasis and those with pathologic Stage IIB disease reached more than 70% in our series. Moreover, two of three patients with cervical lymph node metastasis are still alive more than 3 and 5 years after surgery without recurrent cancer.

While the majority of patients did not have cervical lymph node metastases, the importance of this surgical procedure is in the systematic thorough removal of regional nodes. The most frequent site of lymph node metastasis was the upper mediastinum independent of the primary tumor location. With our dissection of nodes in the lymphadenectomy field done systematically, the survival rates of patients

with positive nodes did not differ from those of patients without nodal metastasis.

High operative morbidity rates following three-field lymph node dissection may be a problem [17–20]. However, in our series, anastomotic leaks, which were the most frequent cause of postoperative complications, healed spontaneously and needed no further surgical intervention. There were no bilateral injuries of recurrent laryngeal nerves. Unilateral vocal cord palsy did not cause life-threatening aspiration as a result of impaired swallowing and was transient. The incidence of vocal cord palsy, caused by thorough lymph node dissection along the recurrent laryngeal nerves, was low as compared with two-field dissection [21]. The meticulous dissection of lymph nodes along the recurrent laryngeal nerves via both transthoracic and cervical approaches could rather avoid injury. Three-field lymph node dissection gave better operative mortality and survival.

In conclusion, we advocate three-field lymph node dissection for patients with clinical Stage I squamous cell carcinomas of the thoracic esophagus because this surgical procedure offers an approximately 70% possibility of cure and favorable survival also for patients with lymph node metastasis.

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