Prognostic Factors in T1 and T2 Squamous Cell Carcinoma of the Thoracic Esophagus

Mitsuo Tachibana, MD; Shoichi Kinugasa, MD; Dipok Kumar Dhar, MD; Hideki Tabara, MD; Reiko Masunaga, MD; Tsukasa Kotoh, MD; Hiroyumi Kubota, MD; Naofumi Nagasue, MD

**Background:** Prognostic indicators in patients with T2 tumor have not been fully understood.

**Objective:** To clarify the clinicopathologic characteristics and long-term results of T1 and T2 squamous cell carcinomas of the thoracic esophagus.

**Design:** Consecutive case series.

**Setting:** Department of surgery in a university hospital.

**Patients:** Of 234 patients with primary squamous cell carcinoma of the thoracic esophagus, 142 patients underwent esophagectomy with curative intent: 97 patients had pT1 and pT2 tumors.

**Interventions:** Investigated were clinicopathologic characteristics of 65 of 97 patients with pT1 and pT2 tumors; excluded were 7 patients who died of postoperative complications and another 25 patients who died of causes other than esophageal cancer.

**Main Outcome Measures:** Clinicopathologic characteristics and long-term results.

**Results:** Pathologic tumor stages were pT1 N0 in 23 patients, pT1 N(+) in 7 patients, pT2 N0 in 15 patients, and pT2 N(+) in 20 patients. Fifty patients are alive and free of cancer and 15 patients died of tumor recurrence (1 patient with pT1 N0 tumor, 1 patient with pT1 N[+] tumor, 1 patient with pT2 N0 tumor, and 12 patients with pT2 N[+] tumor). The sites of metastatic nodes in 6 survivors with pT1 N(+) tumor were a solitary perigastric node in 4 patients, a solitary mediastinal node in 1 patient, and 2 mediastinal nodes in 1 patient. The 5-year survival rates of patients with pT1 N0, pT1 N(+), and pT2 N0 tumors all exceeded 85%, and the rate of those with pT2 N(+) tumor was 33.9% (pT2 N[+] vs others: pT1 N0, pT1 N[+], and pT2 N0; P = .003). The factors affecting survival rate by univariate analysis were Borrmann classification (0, 1 vs 2, 3, 4), tumor size (<4.0 vs ≥4.0 cm), combined T, N factor (pT2 N[+] vs others), time of operation (<420 vs >420 minutes), estimated blood loss (<1000 vs ≥1000 mL), and lymph vessel invasion (marked vs not marked). Stage pT2 N(+) tumor became a single independent prognostic factor for survival as determined by multivariate analysis (pT2 N[+] vs others; P = .008).

**Conclusions:** Stage pT1 N(+) tumors with a few diseased nodes and pT2 N0 tumors are considered to be a group with an excellent prognosis, similar to pT1 N0 tumors. Patients with pT2 N(+) disease had worse prognosis and thus should have meticulous lymph node dissection and extensive adjuvant therapy.

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1.3 Patients with superficial (T1) esophageal carcinoma have a significantly favorable clinical course compared with those with advanced cancers. The outcome for patients with T1 cancer is excellent, with a 5-year disease-specific survival rate exceeding 80%.**4** Conversely, the prognosis of patients with locally advanced (T3 and T4) tumor is far from satisfactory.**7,9** Prognostic indicators, however, in patients with T2 tumor have not been fully understood.

The operative approach for esophageal cancer varies from conventional trans-thoracic esophagectomy chiefly for palliation**10** to wide local excision with extensive lymphadenectomy with curative intent**10** to limited excision without thoracotomy.**31** The confusing factors are that adenocarcinomas of the gastric cardia invading the esophagus and those arising from the Barrett esophagus are reviewed in the literature, but their biologic behavior may be different from that of epider-
PATIENTS AND METHODS

Between December 1979 and November 1997, 234 patients with primary squamous cell carcinoma of the thoracic esophagus were admitted to the Second Department of Surgery, Shimane Medical University, Shimane, Japan. Of these, 142 patients (60.7%) underwent esophagectomy with curative intent: 97 patients (68.3%) had pT1 and pT2 esophageal tumors and the remaining 45 patients (31.7%) had pT3 and pT4 tumors. Of these 97 patients with pT1 and pT2 tumors, excluded were 7 patients (7.2%) who died of postoperative complications during the hospital stay and another 25 patients (25.8%) who died of causes other than esophageal cancer, ie, pneumonia or respiratory failure (5 patients), second cancer (5 patients [hepato-cellular carcinoma in 2 patients and gastric tube cancer, sigmoid colon cancer, and pancreas cancer each in 1 patient]), severe emaciation (4 patients), aging (3 patients), cardiac problems (2 patients), cerebrovascular attack (2 patients), and choking accident, gastric tube ulcer perforation, liver failure, and unknown sudden death at home (each in 1 patient). Therefore, 65 patients were enrolled in this analysis.

Most patients underwent a right transthoracic subtotal esophagectomy and dissection of the cervical (bilateral supraclavicular regions), mediastinal (periesophageus and around the trachea), and abdominal (perigastric lesion and around the celiac axis) lymph nodes. Reconstruction was usually carried out with a gastric tube through the retrosternal route, and esophagogastrostomy was done in the neck under the cervical and abdominal incisions.

When the tumor invaded the deeper submucosal layer, 1 or 2 cycles of adjuvant radiochemotherapy was routinely administered. Patients with T2 tumor received 2 cycles of the same schedule of chemotherapy with radiotherapy. One cycle of chemotherapy consisted of bolus administration of cisplatin (50 mg/m² per day) on the 1st and 15th days and continuous intravenous infusion of fluorouracil (300 mg/m²) for 28 days. One cycle of radiotherapy consisted of 1.8 Gy daily directed to the tumor bed. The total dosage was 30.6 Gy.

Clinicopathologic characteristics of these 65 patients were investigated based on the TNM classification of malignant tumors. The outcomes of patients were examined, and those who clearly died of recurrence were regarded as tumor-related deaths. In calculating the 10-year survival rate, those who were alive more than 10 years were counted as being alive at 10 years.

Survival rates were estimated by the Kaplan-Meier method, and statistical analysis was carried out by the log-rank test to test for equality of the survival curves. In multivariate analysis, independent prognostic factors were determined using a Cox proportional hazards model (StatView J4.5, Abacus Concepts Inc, Berkeley, Calif). The level of significance was P<.05.

RESULTS

Pathologic tumor stages were pT1 N0 in 23 patients, pT1 N(+) in 7 patients, pT2 N0 in 15 patients, and pT2 N(+) in 20 patients. Fifty patients are alive and free of cancer at the time of this analysis. Fifteen patients died because of recurrence: 1 patient with pT1 N0 tumor, 1 patient with pT1 N(+) tumor, 1 patient with pT2 N0 tumor, and 12 patients with pT2 N(+) tumor. The overall 1-, 3-, 5-, and 10-year survival rates of all 65 patients were 91.3%, 77.4%, 72.1%, and 68.1%, respectively.

SITES OF LYMPH NODE METASTASIS IN pT1 N(+) AND pT2 N(+) TUMORS

In 7 patients with pT1 N(+) tumor, the sites of diseased nodes were a solitary perigastric node in 4 patients, a solitary mediastinal node in 1 patient, 2 mediastinal nodes in 1 patient, and multiple cervical and mediastinal nodes in 1 patient who died of recurrence.

In 20 patients with pT2 N(+) tumor, the sites of metastatic nodes were a solitary perigastric node in 4 patients, mediastinal nodes in 4 patients, mediastinal and perigastric nodes in 3 patients, coeliac nodes (M1a) with mediastinal nodes in 4 patients, and cervical (M1a) and mediastinal nodes in 5 patients.

ADJUVANT TREATMENT

Forty-five patients received adjuvant treatment. Of 23 patients with pT1 N0 tumor, 17 patients did not receive any adjuvant treatment and 6 patients received adjuvant radiochemotherapy. Of 7 patients with pT1 N(+) tumor, 6 patients received radiochemotherapy and 1 patient refused any adjuvant treatment. Of 35 patients with pT2 tumor, 25 patients received adjuvant radiochemotherapy and 8 patients with shallow muscle layer invasion received chemotherapy alone. The remaining 2 patients refused any adjuvant treatment.

CUMULATIVE SURVIVAL RATES OF PATIENTS WITH pT1 AND pT2 TUMORS ACCORDING TO LYMPH NODE METASTASIS

The 5-year survival rates of patients with pT1 N0, pT1 N(+), and pT2 N0 tumors were satisfactory, all exceeding 85% (Figure 1 and Figure 2). Conversely, 12 of 20 patients with pT2 N(+) tumor died of recurrence, and the 5-year survival rate was 33.9% (pT2 N[+] vs others: pT1 N0, pT1 N[+], and pT2 N0; P =.003) (Figure 3).

CLINICOPATHOLOGIC FACTORS AFFECTING SURVIVAL RATE

Table 1 shows the clinicopathologic variables affecting the cumulative survival rates by univariate analysis.
The variables affecting survival rate were Borrmann classification (0, 1 vs 2, 3, 4), tumor size (≤4.0 cm), combined T, N factor (pT2 N+ vs others), time of operation (≤420 vs >420 minutes), estimated blood loss (<1000 vs ≥1000 mL), and lymph vessel invasion (marked vs not marked). Sex, histological differentiation, and vessel invasion did not affect the survival rate.

PROGNOSTIC SIGNIFICANCE EVALUATED BY MULTIVARIATE ANALYSIS

Among those 6 significant variables verified by univariate analysis, stage pT2 N(+) tumor was a single independent prognostic factor for survival as determined by multivariate analysis (pT2 N+ vs others; P = .008) (Table 2). Therefore, pT1 N(+) and pT2 N0 diseases are considered to be a group with an excellent prognosis, similar to pT1 N0 tumor.

Depth of invasion is a major denominator deciding the prognosis of esophageal cancer. The prognosis of patients with T1 tumor4-6 is generally good, but the therapeutic result is far from satisfactory for locally advanced (T3 and T4) tumors.7-9 Although patients with T2 tumor are generally considered to have a favorable prognosis, recurrence of the disease occurs in a certain number of patients. Therefore, it is necessary to identify the high-risk group and to design an appropriate therapy for better survival.

The incidence of T1 and T2 esophageal cancer so far reported varies from 13.1% to 52.2%,15-18 and the 5-year survival rate of these patients has been reported to be 22.5% to 88.2%.10,18-20 These data are comparable to the 68.3% incidence of T1 and T2 tumors and 72.1% 5-year survival rate in the present study.

Unlike patients with early gastric carcinoma, the prognosis of patients with esophageal carcinoma is considered to be dismal once the regional lymph nodes are involved.21-23 However, several European series, including that reported by Hoelscher et al,24 found no significant difference in survival between the node-positive and node-negative group in T1 tumor and concluded that nodal status was not an independent prognostic factor by multivariate analysis. Similarly, we demonstrated that there was no significant difference in survival between the pT1 N0 and pT1 N(+) groups, and the 5-year survival rates were excellent, exceeding 85% in both groups. This indicates that a certain number of patients with diseased regional lymph nodes might have excellent survival when the primary tumor is pT1. Also, this survival advantage in patients with pT1 N(+) tumor could be associated with the extent and site of involvement of the regional lymph nodes. In these series, only 1 patient with pT1 N(+) tumor died of recurrence and had extensive lymph node involvement at multiple anatomical fields, and all other surviving patients had only a few (<2) metastatic nodes either in the mediastinum or in the perigastric region. Nishimaki et al25 showed that survival rates of patients with metastases to a single anatomical field were better than those with metastases to 2 fields, similar to another report.26 Moreover, the number of patients who received adjuvant treatment was high (6 of 7 patients) compared with another study.22 Therefore, although the number of patients is small in this study, those with a few metastatic nodes confined to a single ana-

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**Figure 1.** Cumulative survival curves of patients with pT1 esophageal cancer according to lymph node metastasis. The 3- and 5-year survival rates were 100% for those without lymph node metastasis (n = 23) and 85.7% for those with lymph node metastasis (n = 7) (P = .57, log-rank test).

**Figure 2.** Cumulative survival curves of patients with pT2 esophageal cancer according to lymph node metastasis. The 3- and 5-year survival rates were 90% for those without lymph node metastasis (n = 15) and 47.5% and 33.9%, respectively, for those with lymph node metastasis (n = 20) (P = .003, log-rank test).

**Figure 3.** Cumulative survival curves of patients with pT1 and pT2 esophageal cancers according to combined T, N factor. The 3- and 5-year survival rates were 93.8% for those with pT1 N0, pT1 N(+), and pT2 N0 diseases (n = 45) and 47.5% and 33.9%, respectively, for those with pT2 N(+) disease (n = 20) (P = .001, log-rank test).
tumoral region who undergo proper adjuvant therapy are considered to be a group with an excellent prognosis, similar to those with pT1 N0 diseases.

By TNM classification,12 pT1 N0 tumor is classified as stage I and pT2 N0 tumor as stage IIa. Stage pT2 N0 tumors, however, yielded an excellent survival rate that was similar to that of pT1 N0 diseases in the present study. Killinger et al20 compared the survival results in stage II esophageal carcinoma and revealed that survival was not different between T1 N0 and T2 N0 disease (both 50% of 5-year survival rate; \( P = .83 \)). They concluded that the distinction between these subgroups was not warranted. Similarly, Skinner et al19 grouped submucosal (T1) and T2 tumors in 1 group because without any lymph node metastasis, patients with T1 and T2 tumors have similar survival. There are several possible explanations for such contradictory results. First, most reports included patients with esophageal carcinoma of different pathologic backgrounds, for example, squamous cell carcinoma and adenocarcinomas, making the interpretation difficult.10,19,20 Second, we considered only disease-specific deaths to evaluate the prognosis, but most others10,19,20 evaluated the prognosis as overall survival. Last, subtle variations among different institutions, surgeons, or patient characteristics could be another factor. Because our survival data are better than those previously reported, we assume that pT2 N0 disease should be categorized as a group with an excellent prognosis, similar to pT1 N0 tumors.

Our results indicate that pT1 N(+) tumors with a few metastatic nodes confined to a single anatomical region who undergo proper adjuvant therapy are considered to be a group with an excellent prognosis, similar to those with pT1 N0 diseases.

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Our results indicate that pT1 N(+) tumors with a few metastatic nodes confined to a single anatomical re-
gion and pT2 N0 tumors are considered to be a group with an excellent prognosis, similar to pT1 N0 diseases. However, once the tumor was metastasized to the lymph nodes, the prognosis of pT2 tumor became worse. To improve the prognosis of patients with pT2 N(+) tumors, meticulous lymph node dissection and extensive adjuvant therapy might be important.

Reprints: Mitsuo Tachibana, MD, Second Department of Surgery, Shimane Medical University, Enya-cho 89-1, Izumo 693-8501, Shimane, Japan (e-mail: nigeka33@shimane-med.ac.jp).

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