Outcome of Histologically Node-negative Esophageal Squamous Cell Carcinoma

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Abstract. The outcome of node-negative esophageal carcinoma and the prognostic significance of lymph node micrometastasis remain unknown. The aim of this retrospective study was to clarify these two points. A series of 98 patients who underwent curative operation for histologically node-negative (pN0 in TNM classification) esophageal carcinoma were enrolled in the study. We reviewed the cause of death of these patients. The survival curves were calculated and compared after stratifications according to clinicopathologic parameters. Lymph node micrometastasis in the patients with recurrences was examined using immunohistochemical staining of cytokeratin. Their ages ranged from 45 to 83 years (mean 64.3 years). There were 83 men and 15 women. Altogether, 54 patients were still alive, and 44 had died. A total of 9 patients died from recurrence of their esophageal carcinoma, 33 died from other causes (pneumonia 11, extraesophageal carcinoma 7, and so on), and 2 died from unknown causes. Eight patients had locoregional recurrences, and two patients had distant recurrences. The overall survival rate for the 98 patients was 58.2%. The survival for patients with pT2 or pT3 tumors was significantly worse than for those with pT1a or pT1b tumors (p = 0.02, log-rank test). Other clinicopathologic factors did not affect the prognosis. Immunohistochemical study found no lymph node micrometastasis in 365 lymph nodes resected from the patients with recurrences. Only the depth of tumor invasion affected the outcome of patients with node-negative esophageal carcinoma. Altogether, 75% of patients died of other causes without recurrence, with the two main causes of death being pulmonary complications and extraesophageal carcinoma in these patients. Lymph node micrometastasis was not associated with recurrence in this series.

Although operative procedures such en bloc esophagectomy [1] and three-field dissection [2, 3] have been introduced and surgical resection with chemotherapy and irradiation [4] has been carried out, the prognosis for patients with esophageal carcinoma is still poor. Certainly, extended lymph node dissection such as three-field lymphadenectomy has suppressed the frequency of lymphatic recurrence [5], but the overall 5-year survival rate after resection for esophageal carcinoma is still less than 50% [6, 7]. The number of metastatic lymph nodes and the depth of tumor invasion are potential predictors for survival after esophageal carcinoma [8]. The outcome of patients with multiple metastatic nodes is poor even after extended lymph node dissection [9]. The prognosis for patients without metastatic lymph nodes is better than that for patients with multiple metastatic nodes [9]; however, the postoperative outcome of these patients has not been investigated in detail. Moreover, the prognostic significance of lymph node micrometastasis is still controversial for those with node-negative esophageal carcinoma. The aims of this retrospective study were to review the outcome of histologic node-negative esophageal carcinoma and to examine the relation between lymph node micrometastasis and recurrence using immunohistochemical studies.

Materials and Methods

Patients

From January 1983 to December 1999 a series of 303 patients with carcinoma of the thoracic esophagus underwent esophagectomy at the Department of Surgery I, Kumamoto University Hospital, Kumamoto, Japan. Among them, 98 patients with pN0M0 esophageal squamous cell carcinoma (TNM classification) [10] were enrolled in this study. These patients underwent radical esophagectomy (R0 resection, TNM classification). There were 83 men and 15 women with an age range of 45 to 83 years (mean 65.3 years). The indications for preoperative chemotherapy were as follows: In principle, no patients with carcinoma in situ were given chemotherapy; most patients with a T1 tumor received preoperative chemotherapy, as did all of the remaining patients (T2, T3 tumors). As reported previously, we introduced preoperative chemotherapy in 1983 [11], giving it based on chemosensitivity testing of esophageal cancer cells obtained by preoperative endoscopic biopsy [12, 13]. A single course of preoperative chemotherapy and one or two courses of postoperative chemotherapy were carried out. Patient refusal and postoperative major complications (pneumonia, anastomotic leakage, sepsis) accounted for most cases of discontinuance or were contraindications for postoperative chemotherapy [13]. According to this protocol, 17 patients underwent both preoperative and postoperative chemotherapy; 17 received preoperative chemotherapy alone, 10 were given postoperative chemotherapy alone, and the remaining 54 patients underwent surgery alone. No patients with p-stage 0 tumor, 11 with p-stage I tumor, and 23 with p-stage IIA tumor received preoperative chemotherapy. In contrast, 9 patients with p-stage 0, 43 with
were evaluated by CT scans, operation, or autopsy. The presence of lymph node micrometastasis in these patients using immunohistochemical studies. We examined 365 lymph nodes resected from 10 patients with recurrence of esophageal carcinoma in this study. In brief, five representative sections of each tissue block of lymph node were used for this staining. These sections were deparaffinized in xylene and alcohol and rinsed in phosphate-buffered saline (PBS). After these steps, the sections were incubated with AE1/AE3 at 1:200 dilution for 30 minutes at room temperature. After rinsing in water and cooking in PBS buffer, the sections were covered with a droplet of Envision and incubated for 30 minutes at room temperature. We used metastatic lymph node diagnosed by hematoxylin and eosin (H&E) staining as a positive control.

Lymph node micrometastasis was defined as the presence of immunoreactive atypical epithelial cells in the subcapsular sinus or the cortex of the lymph node [14]. We excluded metastasis found by routine pathologic examination of a micrometastasis. Two investigators (Y.T. and M.Y.) examined the specimens for the presence of micrometastasis in a blinded fashion.

Methods

Preoperative staging was done by barium swallow, esophagoscopy, endoscopic ultrasonography, and computed tomography (CT) scans. The depth of tumor invasion (pT) was evaluated by pathologic TNM classification, 9 patients had pTis tumors, 54 had pT1 tumors, 13 had pT2 tumors, and 22 had pT3 tumors. The postoperative follow-up ranged from 0 to 168 months (median 48 months). Ten patients had associated synchronous or asynchronous extraesophageal malignant tumors (two synchronous, eight asynchronous).

Outcomes were that 54 patients were alive and the other 44 patients had died. Ten patients suffered from relapse of their esophageal carcinoma; one is still alive, and the rest died within 3 years after esophagectomy. Altogether, 33 patients died of other causes, and 2 patients died of unknown causes.

Results

Outcome

The 5-year survival rate for all subjects was 58.2%. The 5- and 10-year survival rates for subgroups according to the clinicopathologic variables are shown in Table 1. The survival rate for patients with pT2 or pT3 tumors was worse than that for patients with pTis or pT1 tumors at any time point. The survival of patients who underwent preoperative or postoperative chemotherapy (or both) was significantly worse than that of patients who did not receive preoperative/postoperative chemotherapy. The remaining eight factors (age, gender, site of tumor, lymphatic invasion, vessel invasion, histologic grade, three-field lymphadenectomy or not, the presence of extraesophageal cancer) did not affect the outcome of patients with histologically node-negative esophageal carcinoma. The 5-year survival rate for pT2 or pT3 tumors was 49.2% but 63.6% for pTis or pT1 tumors (p = 0.02, log-rank test) (Fig. 1).