Late toxicity in complete response cases after definitive chemoradiotherapy for esophageal squamous cell carcinoma

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Introduction

In Western countries, the number of patients with esophageal adenocarcinoma has been increasing, whereas most patients in Japan have squamous cell carcinoma of the esophagus. Previous studies indicated that 95% of esophageal cancers in Japanese patients are squamous cell carcinomas.¹ In recent years, most patients are still diagnosed with advanced-stage ESCC, although the number of patients found with early-stage ESCC has been increasing. The standard therapy in Japan for patients with resectable disease has been surgery. The 5-year survival rate for T1, T2, and T3 disease was 52%, 37%, and 28%, respectively.²

On the other hand, the effects of chemotherapy combined with radiotherapy on esophageal carcinoma have been investigated since the 1980s. Several investigators have reported successful results with these modalities, either with or without surgery, against locoregional carcinoma.³⁻⁸ The combination of 5-fluorouracil (5-FU) and cisplatin (CDDP) has become a standard regimen, not only because of the clinical outcome, but also because of the synergism between the two agents and their radiosensitizing effects.⁹⁻¹¹ Recently published results on chemoradiotherapy (CRT) indicated that it offers various advantages for the treatment of carcinoma of the esophagus.⁷,¹² In a prospective randomized trial by the Radiation Therapy Oncology Group, which compared chemoradiotherapy with radiotherapy alone, the combined-modality arm demonstrated a significant improvement of survival;¹³ with a 5-year survival rate of 27%, compared with 0% for radiotherapy alone.¹⁴ With regard to the indications for CRT as a curative treatment for patients with locally advanced diseases, our multicenter study suggested that concurrent CRT was potentially curative even in cases with unresectable carcinoma of the esophagus (i.e., T4 and/or M1 LYM disease).¹⁵,¹⁶

Esophageal cancer deaths often occur in non-CR cases or in recurrent cases. However, recent data indi-
cate that the risk of early death from esophageal carcinoma is not quite as daunting for patients who achieve complete response (CR) after CRT. We have already reported that concurrent CRT was effective for inoperable patients. Therefore, a significant proportion of CR patients may have a sufficiently long survival time to allow for the adequate assessment of treatment-related late toxicity. We retrospectively investigated the long-term toxicity after definitive CRT for patients with squamous cell carcinoma of the thoracic esophagus.

Methods

Patient population

From May 1996 through March 2002, 110 consecutive patients were diagnosed at Showa University School of Medicine as having esophageal carcinoma. Patients were recruited from our database on the basis of the following criteria: age ≤ 75 years, performance status (Eastern Cooperative Oncology group) 0 to 2, clinical stage I to IVA (International Union Against Cancer tumor-node-metastasis system, 1997), adequate organ function, and no other site of carcinoma except for early stage. None of the patients had surgery or chemotherapy for previous diseases. In agreement with that observation, none of the patients enrolled in this study had esophageal adenocarcinoma; thus, all patients had squamous cell carcinoma of the esophagus.

Eligibility criteria

Patients who were eligible for this trial had previously untreated, histologically confirmed squamous cell carcinoma of the thoracic esophagus. The tumors had to show evidence of T1–T4 disease, containing M1 LYM disease, based on the staging criteria of the UICC. The prestudy clinical evaluation included air-contrast barium esophagography, esophagoscopy, neck computed tomography (CT), chest CT, abdominal CT, endoscopic ultrasonography (EUS), bronchoscopy, and bone scan. However, EUS was optional because the endoscope could not be passed through stenotic lesions in most cases (68%). Bronchoscopy was performed in some cases when tracheobronchial involvement was suspected. Because the prognosis of patients with T4 disease differed significantly from that of patients with T3 disease,16 we defined T3 and T4 disease in clinical staging. Adjacent organs were considered to be involved (T4 disease) if the tumors extended into the esophageal lumen, or caused deformity of the tracheobronchial tree, or if the tumors appeared to be attached to the organs at >90° angle to the thoracic aorta as observed on the CT scan.17,18 T3 or lesser extent of the disease was determined by EUS. In those patients who could not undergo this procedure, T3 was defined based on the lack of any associated abnormal bronchoscopic findings; i.e., no deformity of the airway and tracheobronchial tree on the CT scan. Furthermore, we modified the criteria described previously for the definition of T3 disease17 to include tumors attached to the organs at ≤90° angle to the thoracic aorta as observed on the CT scan. The patients were considered to have lymph node metastasis if the tumor was ≥1 cm in diameter.19 Radiologic evaluations for staging were reviewed by radiologists and medical oncologists at Showa University School of Medicine, as was reported in previous studies.17–19 However, although the UICC staging criteria were adopted in these previous studies, we used a nonstandard staging technique in this study, especially when evaluating the depth of tumor infiltration.

The following criteria were used for enrollment for chemoradiotherapy: (1) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or less, (2) satisfactory hematological function (leukocyte count ≥3000/mm³ and platelet count ≥100,000/mm³), (3) satisfactory hepatic function [aspartate aminotransferase (AST) or alanine transferase (ALT) levels within three times the normal upper limit and a serum bilirubin level <2.0 mg/dl], (4) good renal function (creatinine level ≤1.5 mg/dl and creatinine clearance ≥50 ml/min), (5) satisfactory pulmonary function (PaO₂ ≥ 70 mm Hg), (6) normal electrocardiogram, and (7) life expectancy ≥8 weeks. Patients with serious complications, such as history of ischemic heart disease, pulmonary fibrosis, or active carcinoma at another site, were excluded from the study. After explaining the true disease status and predicted complications of the treatment, including the possibility of treatment-related death, each patient gave informed consent for the study. The study protocol was approved by the Human Ethics Review Committee of Showa University School of Medicine.

Treatment schedule

Chemotherapy consisted of protracted infusion of 5-FU at a dose of 400 mg/m² per day on days 1–5 and 8–12, combined with 2-h infusion of CDDP at 40 mg/m² on days 1 and 8 (Fig. 1). A 10-MV radiation treatment was administered for 3 weeks (5 days/week) at 2 Gy/day, concomitantly with chemotherapy. The targeted area for carcinoma of the upper and middle third of the esophagus included the primary tumors with a 3-cm margin craniocaudally and any metastatic nodes with 1- to 1.5-cm margin, in the supraclavicular fossa and mediastinum. For carcinoma of the lower third of the esophagus, the field was extended to include the