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Esophageal cancer radiotherapy

# Retrospective analysis of definitive radiotherapy for patients with superficial esophageal carcinoma: Consideration of the optimal treatment method with a focus on late morbidity

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ABSTRACT

*Purpose:* To evaluate the clinical efficacy of definitive radiotherapy for patients with superficial esophageal cancer.
*Material and methods:* From 1990 through 2006, 97 patients with stage I disease were treated with radiotherapy with or without chemotherapy. All patients were diagnosed with panesophagoscopy and computed tomography. Chemotherapy was added in 61 patients, and intra-cavitary brachytherapy (ICBT) was used in 27 patients.
*Results:* The patients were 90 men and seven women with a median age of 65.7 years (range; 41–89). At last follow-up with a median follow-up duration of 35.7 months, 3 year-overall and progression-free survival (PFS) rates were 81.5% (95% C.I. = 73.3–89.7%) and 55.8% (95% C.I. = 45.2–66.4%), respectively. Shorter tumor length was a significantly favorable factor for the PFS rate ($P = 0.02$) and local failure-free (LFF) rate ($P = 0.007$) on both univariate and multivariate analyses. Although the addition of ICBT had no apparent benefit for survival or tumor control, the rate of severe adverse effects including lethal esophageal ulcers, showed a higher tendency in patients receiving ICBT.
*Conclusions:* Our results regarding efficacy from the viewpoint of organ preservation are promising. Special care would be taken for the use of ICBT for patients with superficial esophageal cancer, especially if they have received chemoradiotherapy.
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Esophageal cancer still remains disease with high mortality despite recent improvements in diagnosis and treatment. The mortality rate for Japanese patients with esophageal cancer is 9.0 per 100,000 (15.7 per 100,000 in males, 2.6 per 100,000 in females), representing 3.4% (4.9% in males, 1.3% in females) of all deaths by malignant neoplasms in 2006 [1]. Mortality rate of esophageal cancer has increased slightly over the past two decades. Although half of patients have adenocarcinoma in Western countries, the majority of patients in Japan have squamous cell carcinoma.

In recent years, the number of patients with stage I disease, in which the primary lesion is limited to the mucosal layer of the esophagus, has increased. According to the third Comprehensive Registry of Esophageal Cancer in Japan, in 1999 clinical stage I disease (T1N0M0) accounted for 20.1% of all cases, 12.3% of cases in patients treated with radiotherapy or chemoradiotherapy, and 20.1% of cases in patients treated with esophagectomy [2]. The reported number of patients undergoing esophagectomy is more than 3.6 times the number of patients receiving radiation or chemoradiation therapy (365 vs. 103).

In Japan several retrospective studies [3–7] have shown promising clinical outcomes of definitive radiotherapy for early stage disease of the esophagus, and because the trend in Japan for a less-toxic treatment, definitive radiotherapy has become a standard treatment for patients with stage I esophageal cancer. The Japan Clinical Oncology Group is leading a randomized controlled trial (JCOG0502) to compare the clinical outcomes of surgery and chemoradiotherapy for patients with stage I esophageal cancer.

Since 1990, more than 100 patients with stage I disease have received definitive radiotherapy at our hospital. To evaluate its clinical efficacy, we retrospectively analyzed clinical outcomes of this cohort according to disease characteristics and treatment contents.

## Materials and methods

### *Eligibility criteria*

From 1990 through 2006, 97 patients with histologically confirmed stage I squamous cell carcinoma of the esophagus

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diagnosed according to the criteria of the International Union Against Cancer, sixth edition (2002), were eligible for this analysis. The laboratory examinations consisted of complete blood count (CBC), serum chemistry, 24 h creatinine clearance, arterial blood gas, electrocardiography, and pulmonary function tests. The staging work-up included chest radiography; computed tomography (CT) of the cervix, chest, and abdomen; esophagography; and panesophagoscopy with iodine staining. In a selected case diagnosed as having submucosal layer disease ($n = 12$), the endoscopic ultrasonography (EUS) was also used to help the evaluation of tumor depth. In weekly conference, disease stage including the depth of tumor invasion is usually determined by institutional tumor board consisted of surgeon, medical physician, radiologists, and radiation oncologists. Considering our sufficient diagnostic quality for tumor depth (>90%) by assessing surgical findings, we did not use EUS for all cases. After May 2002, positron emission tomography (PET) or PET/CT was used for staging work-ups. Lymph node swelling of 10 mm or more along the long axis was found in no patient on CT scan.

### *Chemotherapy*

Sixty-one of the patients had submucosal disease and, because laboratory studies indicated a sufficiently good general condition, received systemic chemotherapy. Thirty-nine patients received two cycles of fluorouracil (5-FU) and cisplatin administration via intravenous infusion every 4 weeks. Elderly patients and patients with medical illness ($n = 8$) received radiotherapy and protracted daily low-dose chemotherapy with 5-FU or cisplatin or both during external beam radiotherapy (EBRT). Seven patients with simultaneously diagnosed head and neck squamous cell carcinoma received intravenous 5-FU and nedaplatin with an alternating setting. The details of this protocol have been reported elsewhere [8]. Thirty-six patients received only radiation therapy without systemic chemotherapy.

Patients with mucosal disease ($n = 24$) received radiotherapy alone, because lymphatic spread is thought to be rare for such patients.

### *Radiotherapy*

Radiation therapy with a megavoltage photon beam (6 or 10 MV) was started on day one of systemic chemotherapy. The gross tumor volume (GTV) was defined as the total volume of the primary tumor. Before taking a simulator film or planning CT, the esophageal lesion was marked with a metallic clip to indicate the cranio-caudal extent.

The clinical target volume (CTV) was defined as the GTV with a 2 cm margin in the longitudinal direction. No prophylactic lymph node region was included in the CTV. The planning treatment volume (PTV) of the primary tumor was defined as the CTV with a 1–1.5 cm cranio-caudal margin and a 0.5–1 cm lateral margin. Radiotherapy was given with a daily 2 Gy fraction to a total dose of 60 Gy. For patients who did not receive chemotherapy, the proposed dose was designed to be 66 Gy. Initially, a dose of 40 Gy to the PTV was planned for 1–4 weeks, using anteroposterior parallel opposed pairs of portals. Then, another 20 Gy was applied to the PTV with a proper margin in an oblique parallel opposed manner or with the dynamic conformal method during fifth and sixth weeks. The spinal cord never received more than 45 Gy. The radiation dose and the volume to the lung and heart were minimized in each case.

Until 2004, patients with submucosal lesions shorter than 5 cm received intra-cavitary brachytherapy (ICBT) after the completion of EBRT with 46–56 Gy [9]. Twenty-seven patients received ICBT with a radium ($n = 3$) or iridium source ($n = 24$). High-dose-rate (HDR)–ICBT was performed with a remote-after-loading system using an iridium source. A double-balloon applicator system [10] was used in patients treated with HDR–ICBT. Five patients also received intra-cavitary hyperthermia [11] along with ICBT. ICBT was performed immediately after the completion of EBRT. The median dose of ICBT was 10 Gy (range, 4–20 Gy). The 2–5 fractions with 3–5 Gy per fraction were usually used in their series. The estimated dose was calculated 5 mm beyond the surface of the double-balloon applicator [4,10]. Only four patients received relatively higher radiation dose of 80 Gy (60 Gy of EBRT and 20 Gy of ICBT), otherwise majority patients ($n = 88$, 91%) received total dose (EBRT + ICBT) with a range from 54 Gy to 66 Gy. To appropriately evaluate for dose impact for late mucosal reaction by both EBRT and ICBT, we have also calculated $EQD_2$ which is the calculated biological dose equivalent, as if 2 Gy per fraction would have been applied. As for estimate of late adverse event, alpha/beta value of three was used for estimate of late mucosal and submucosal reactions.

### *Follow-up*

Patients were followed up at 2–3 months intervals for the first 2 years and at 4–6 months intervals thereafter. Follow-up examinations included physical examinations, CBC, chemistry profiles including tumor markers, esophagoscopy, and CT of the neck, chest, and abdomen.

Treatment response was evaluated 1 month after the completion of radiation therapy. Usually, patients underwent esophagoscopy and CT of the neck, chest, and abdomen 1 month after the completion of the treatment session.

### *Statistical considerations*

The survival time was defined as the period from the start of treatment to death or the last follow-up evaluation, and progression-free survival (PFS) was defined as the period from the start of treatment to progression of disease (PD) or death for any reason. Development of second primary was not considered an event for PFS. New esophageal cancer out of radiation field was excluded from second primary. The local failure-free (LFF) time was defined as the period from the start of treatment to the failure of the esophagus within the radiation field. Newly esophageal cancer out of radiation field was counted as event for disease progression, but not for local failure. Statistical differences between groups were assessed with the $x^2$ test. The overall survival (OAS) and PFS curves were calculated using the Kaplan–Meier method [12]. The log-rank test [13] was used to compare survival curves. Cox's proportional hazard model [14] was used for multivariate analysis. Prognostic factors selected for univariate and multivariate analyses, included patient age, sex, tumor length, tumor location, mucosal or submucosal lesion, solitary or multicentric lesion, coexistence of second primary, use of ICBT, and use of chemotherapy.

## Results

### *Patient's characteristics and treatment contents*

Patients' characteristics and treatment contents are summarized in Table.1. Seventeen patients had undergone endoscopic mucosal resection (EMR) for esophageal disease with mucosal lesions before consultation for definitive radiotherapy. Seventy-one (73.2%) patients underwent consultation for radiotherapy because radical surgery could not be performed owing to second primary or poor general condition or both. Twenty-six (26.8%) patients who were considered contradiction for radical surgery hoped to receive chemoradiotherapy.