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Long-term outcomes of combined endoscopic resection and chemoradiotherapy for esophageal squamous cell carcinoma with submucosal invasion

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ABSTRACT

Background: For esophageal squamous cell carcinoma (ESCC) with submucosal (SM) invasion, surgery is the standard treatment. Definitive chemoradiotherapy (D-CRT) is a less invasive alternative option, but sometimes results in locoregional failure.
Aim: To examine whether endoscopic resection for primary lesion removal combined with chemoradiotherapy (ER-CRT) reduces locoregional failure rates in cases of ESCC with SM invasion.
Methods: We retrospectively compared clinical outcomes between ER-CRT and D-CRT in patients diagnosed with ESCC with SM invasion between 2003 and 2014. Twenty-one patients underwent ER-CRT based on a pathological diagnosis, and 43 patients underwent D-CRT based on a clinical diagnosis.
Results: Locoregional failure developed in 26% of patients in the D-CRT group, and in no patients in the ER-CRT group ($p < 0.01$). Thus, the 5-year relapse-free survival in the ER-CRT group was significantly more favorable than that in the D-CRT group (85.1% vs 59.2%; $p < 0.05$), although there was no difference in overall survival (85.1% vs 79.1%) nor in cause-specific survival (90.5% vs 87.2%) between the groups. There were no instances of perforation or hemorrhage associated with ER.
Conclusion: ER-CRT is a safe and effective treatment strategy and can be considered as a new minimally invasive treatment option for patients with ESCC with SM invasion.

1. Introduction

Esophageal cancer is the seventh most common malignancy and the sixth leading cause of cancer death worldwide [1]. Using the TNM (tumor, node, metastasis) classification of malignant tumors, T1-esophageal squamous cell carcinoma (ESCC) is further divided into T1a (tumor invading the lamina propria mucosa to the muscularis mucosa) and T1b (tumor invading the submucosa) [2]. Endoscopic resection (ER) is commonly performed for T1a-ESCC, while the standard treatment for T1b-ESCC is surgery with extended lymph node dissection due to its associated high incidence of lymph node metastasis [3–6]. Therefore, ER alone for T1b-ESCC cannot be considered curative and the standard treatment for submucosal (SM) cancer is surgery [7]. The overall survival (OS) of T1-ESCC patients who underwent surgery was over 80% at 3 years [8,9]. However, surgery is highly invasive, associated with increased mortality, and often adversely affects the patient's general physical condition, particularly if they are elderly.

A Japan Clinical Oncology Group (JCOG) phase II trial (JCOG 9708) found that in T1-ESCC patients, the survival rate following definitive chemoradiotherapy (D-CRT) was comparable to that after surgery, with a 4-year survival rate of 80.5%. D-CRT has therefore been shown to improve survival rates of T1-ESCC patients and is increasingly being considered as a less invasive treatment option [10]. However, its higher risk of locoregional failure compared with surgery remains a concern [11].

It is often difficult to precisely evaluate the invasion depth in superficial ESCC before surgery and D-CRT [12]. However, recent advances in endoscopic diagnosis using magnifying endoscopy with narrow-band imaging (NBI) and endoscopic ultrasonography

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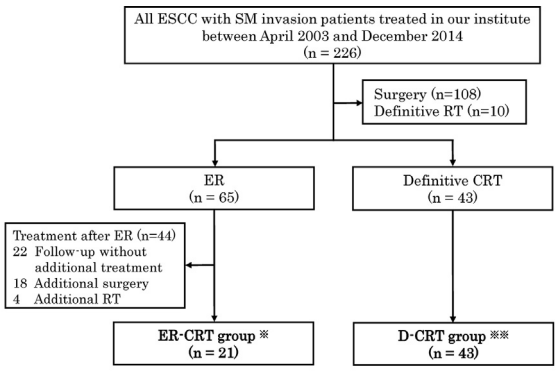

Fig. 1. Flowchart shows the management of esophageal squamous cell carcinoma (ESCC) with submucosal (SM) invasion in our institute.

(EUS) have improved the diagnostic accuracy of determining the invasion depth [13,14]. In the setting of a clinical diagnosis of T1b-ESCC, the pathological results following surgery sometimes indicate T1a-ESCC, which means that unnecessary surgery has been performed. Recent advances in ER, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), have enabled the effective removal the primary lesions. In particular, ESD has a significantly high R0 resection rate [15]. By resecting the primary lesions, we can obtain a more accurate assessment of invasion depth of ESCC and thus select the most appropriate treatment strategy.

Shimizu et al. performed a confirmatory study of combined ER and chemoradiotherapy (ER-CRT) for T1-ESCC. They reported a 5-year OS of 100% with no instances of locoregional failure; however, many of the included cases were ESCC with muscularis mucosa invasion [16]. It has been reported that clinical outcomes after ER alone for muscularis mucosa invasion cases are generally favorable [17,18]. On the other hand, there are very few reports on clinical outcomes of ER-CRT for ESCC cases with SM invasion. In this retrospective study, we compared the efficacy, safety, and long-term outcomes associated with ER-CRT or D-CRT in patients with ESCC with SM invasion.

2. Materials and methods

2.1. Patients

In our institution, 226 patients with ESCC with SM invasion were treated between April 2003 and December 2014. Among the 226 patients, 108 underwent surgery, 65 underwent ER, 43 received D-CRT, and 10 received definitive radiotherapy (RT). Among the 65 patients who underwent ER, 22 were followed-up without additional treatment, 21 received additional CRT, 18 underwent additional surgery, and 4 received additional RT after ER. We analyzed and compared clinical outcomes between the 21 patients who underwent ER and additional CRT based on a pathological diagnosis (ER-CRT group) and the 43 patients who received D-CRT based on a clinical diagnosis (D-CRT group) (Fig. 1). The decision to pursue a particular treatment option was made based on the patients' condition and their personal preference for a treatment strategy. A clinical diagnosis of ESCC with SM invasion was confirmed using high-resolution endoscopy with magnifying endoscopy with NBI, iodine staining, and EUS. Before undergoing treatment, the absence of detectable lymph node and distant metastases were confirmed using neck to abdominal computed tomography (CT) scans.

All patients provided written informed consent. The institutional review board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research approved this study (IRB No. 2016-1053). The study was conducted in accordance with the Declaration of Helsinki 1964 and its later amendments.

2.2. ER procedure and treatment protocols after ER

Until 2010, we treated patients mainly with EMR using a cap-fitted endoscope (EMR-C). ESD was initiated in 2008 and most patients from 2011 onwards were treated with ESD.

ER specimens were microscopically examined by certified pathologists of the Japanese Society of Pathology and evaluated according to the Japanese Classification of Esophageal Cancer, 11th edition [6]. For each cancer, we determined predictive factors for lymph node metastasis which included the histological type, invasion depth, lateral and vertical resection margins, and the presence of lymphovascular invasion and droplet infiltration (DI) [19]. In patients with SM1 (<200 μm of SM invasion) without lymphovascular invasion, DI, and a negative resection margin, we recommended no additional treatment. In patients with SM2 or greater (>200 of μm SM invasion), lymphovascular invasion or DI, and/or positive resection margins, we recommended surgery or CRT as additional treatments after ER. The decision on whether to proceed with additional treatment or to monitor without additional treatment was made after considering the pathological diagnosis, the patients' condition, and their personal preference for a treatment strategy.

2.3. Chemoradiotherapy

The chemotherapy regimen involved a continuous infusion of 5-fluorouracil (5-FU) (700 mg/m^2/day for 24 h) on days 1–4 and 29–32 and administration of cisplatin (CDDP) (70 mg/m^2) days 1 and 29. For patients with raised creatinine levels (≥1.3 mg/dL), the CDDP dose was reduced by 50%. RT was delivered with megavoltage (MV) equipment (≥6 MV) (Clinac 21EX, Varian Medical Systems, Inc., Palo Alto, CA, USA) with anterior/posterior opposed and bilateral oblique portals. RT planning was carried out with a CT-simulator and RT planning system (Eclipse, Varian Medical Systems, Inc.). The clinical target volume (CTV) included the regional nodal area as follows: (1) for the cervical/upper thoracic esophagus, the area included the supra-clavicular, upper mediastinal and sub-carinal nodal areas; (2) for the middle thoracic esophagus, the area included the mediastinal and perigastric nodal areas; (3) for the lower thoracic/abdominal esophagus, the areas included the mediastinal, the perigastric and celiac nodal areas.

In the ER-CRT group, CRT as an additional treatment was initiated 1 or 2 months after ER and after confirmation of the post-ER ulcer healing. The dose of RT was 41.4 Gy/23 fractions/5 weeks (5 days/week), including the regional nodal area. For patients with a positive resection margin by pathological diagnosis after ER, further 9 Gy boost irradiation to the primary site was applied. In the D-CRT group, the dose of RT was 60 Gy/30 fractions/5 weeks (5 days/week), 40 Gy was applied to the regional nodal area, and 20 Gy was applied as boost irradiation to the primary site.

Toxicities were scored in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE ver. 4.0).

2.4. Follow-up and evaluation of recurrence

Patients were followed-up with blood tests including tumor marker measurements, esophagogastroduodenoscopy (EGD), and neck to abdominal CT at least every 6 months for 5 years after treatment. Response to treatment was assessed using EGD, and

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