

Clinical Outcomes of Esophagectomy and Chemoradiotherapy After Endoscopic Resection for Superficial Esophageal Squamous Cell Carcinoma

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Abstract. *Background/Aim: Surgical resection and chemoradiotherapy (CRT) can be performed as additional treatments for superficial esophageal cancer after endoscopic resection, but the selection criteria vary depending on the institution. We retrospectively evaluated the outcomes of patients with endoscopically resected superficial esophageal cancer treated with surgical resection and CRT at our institution. Patients and Methods: The outcomes of 67 cases of additional treatment after endoscopic resection of superficial esophageal cancer, excluding adenocarcinoma, performed at our hospital from January 2000 to June 2017 were compared (30 cases in the surgery group and 37 cases in the CRT group). Results: In the surgery group, eight patients had lymph node metastasis and two had recurrence in the supraclavicular fossa lymph nodes after surgery, therefore reoperation was performed. There were no deaths from esophageal cancer, and the 5-year survival rate was 92.6%. One patient in the CRT group had a recurrence in the cervical paraoesophageal lymph node, which was resected, but no death from esophageal cancer was observed, and the 5-year survival rate was 81.0%. The 5-year survival rate was significantly better in the surgery group than in the CRT group ($p=0.039$). The greater number of elderly patients in the CRT group was considered to be the reason for the worse prognosis. Conclusion: Although the prognosis of esophagectomy or chemoradiotherapy (CRT) is very favorable, CRT is considered to be the preferred additional treatment after endoscopic resection of superficial esophageal cancer without lymph node metastasis from the viewpoint of organ preservation.*

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The diagnosis of superficial esophageal cancer has been increasing in Japan due to the increase in the number of endoscopic examinations and the improvement of endoscopic image quality (1). Although esophagectomy is the standard treatment for superficial esophageal cancer with clinically suspected submucosal invasion, pathological examination after resection often reveals intramucosal cancer without lymph node metastasis (2).

In recent years, endoscopic resection has become widely used for the diagnosis and treatment of superficial esophageal cancer without lymph node metastasis because of improvements in endoscopic technology that enable *en bloc* resection of lesions. If the pathological examination after resection shows that there is a possibility of lymph node metastasis based on the depth of the primary lesion and findings of vascular invasion, additional treatment is required (3-5). In general, additional treatment is required for T1a cancers with positive vascular invasion, submucosal invasion, and positive resection margins.

Esophagectomy has been commonly used as an additional treatment after endoscopic resection of superficial esophageal cancer. However, patients with superficial cancer of the esophagus who undergo surgical resection have comparable outcomes to those undergoing CRT. Therefore, an increasing number of institutions have CRT as an additional treatment, and favorable outcomes have been reported. However, the choice of surgery or CRT as additional treatment varies among institutions and physicians. In this study, we retrospectively evaluated the outcomes of patients with endoscopically resected superficial esophageal cancer treated with surgical resection and CRT at our institution.

Patients and Methods

The outcomes of 67 patients who received additional treatment after endoscopic resection of superficial squamous cell carcinoma of the esophagus, excluding adenocarcinoma, at our hospital between

January 2000 and June 2017 were evaluated in two groups: a surgery group (n=30) and a CRT group (n=37). Endoscopic resection (ER) was performed using endoscopic mucosal resection until 2007, and endoscopic submucosal dissection (ESD) has been performed since 2007. Resection specimens were cut at 2-mm intervals according to the guidelines established by the Japan Esophageal Society (6), and pathologists judged the depth, horizontal and vertical margins, and the presence of vascular invasion in each lesion. Before endoscopic resection, all patients were confirmed to be negative for lymph node metastasis and distant metastasis by computed tomography scan.

In endoscopic resected specimens, submucosal (SM) infiltration was divided into two groups, depending on the extent of infiltration, and based on the Japanese guidelines, as follows: tumors infiltrating ≤200 mm from the lower end of the mucosal muscle plate were classified as pSM1, and those extending >200 mm were classified as pSM2. For lesions with a depth of the mucous membrane or more, surgery or CRT was performed. Patients who were considered by the physicians to be unsuitable for surgery due to old age, complications, or other reasons were chosen to receive CRT, whereas for patients who could tolerate surgery, the patients themselves chose whether to undergo surgery or CRT. Surgery was performed by a right lateral thoracotomy or thoracoscopic subtotal esophagectomy. Cervical lymph node dissection was performed only in cases where the primary tumor was located at the upper thoracic esophagus. The pathological stage was determined according to the eighth edition of the tumor–node–metastasis classification established by the Union for International Cancer Control.

Radiotherapy was administered using a megavoltage photon beam (6-18 MV). The clinical target volumes included the supraclavicular, upper mediastinal, and middle mediastinal lymph nodes for upper thoracic tumors and the upper to lower mediastinal and perigastric lymph nodes for middle thoracic or lower thoracic tumors (7). The dose of radiotherapy was 60 Gy in 2.0 Gy per fraction. The spinal cord never received >40 Gy in either plan.

The regimen of chemotherapy was as follows: CF (Cisplatin 70 mg/m² on days 1 and 29 and 5-Fluorouracil 700 mg/m² on days 1-4 and 29-32). At the discretion of the attending physician, nedaplatin was administered instead of cisplatin in patients with renal hypofunction. All patients who underwent CRT were able to complete the procedure.

All patients underwent medical examination, blood examination, and CT imaging every 6 months for at least 5 years after surgery and endoscopy annually. If any symptoms were reported, a more detailed examination was performed.

All analyses were performed with the SPSS® software program, ver. 26 (IBM, Armonk, NY, USA), and *p*-values of <0.05 were considered significant. The study protocol was approved by the Ethics Committee of Hiroshima University Hospital (IRB number 3280).

Results

Patient characteristics. The clinical features and pathological findings of the 67 patients who underwent esophagectomy or CRT after endoscopic treatment are shown in Table I. Thirty patients underwent surgery and 37 received CRT. The median age of the surgery group was 62 years, and the median age of the CRT group was 66 years (*p*=0.017). All patients had cN0 disease, and there were no differences between the two groups in terms of sex, site of tumor occupation, depth, or vascular

Table I. Baseline characteristics of the 67 patients.

	Esophagectomy group (n=30)	CRT group (n=37)	<i>p</i> -Value
Age-yr			0.017
Median	62	66	
Range	54-78	57-81	
Sex			0.283
Male	25	34	
Female	5	3	
Endoscopic treatment			0.102
EMR	12	8	
ESD	18	29	
Location of tumor			0.627
Ce	1	4	
Ut	4	4	
Mt	16	20	
Lt	9	8	
Ae	0	1	
Depth of tumor			0.457
M3	6	12	
SM1	7	9	
SM2	17	16	
Lymphatic invasion			0.746
Positive	11	15	
Negative	19	22	
Venous invasion			0.811
Positive	5	7	
Negative	25	30	
Horizontal margin			0.028
Positive	3	9	
Negative	27	28	
Vertical margin			0.212
Positive	5	8	
Negative	25	29	

CRT: Chemoradiotherapy; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; Ce: cervical esophagus; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; Ae: abdominal esophagus.

invasion, but there were significantly more patients with positive horizontal margins in the CRT group.

Clinicopathological features and postoperative complications after esophagectomy. Of the 30 patients who underwent surgical resection, 8 had lymph node metastasis. Two patients developed recurrence, both of which were supraclavicular lymph node recurrences that could be surgically resected. In both patients, lymph node dissection was performed followed by postoperative CRT to both supraclavicular fossa lymph nodes. There was no distant metastasis in any patients who underwent surgical resection, and there was no death from esophageal cancer (Table II). Postoperative complications within 30 days included pneumonia in four patients (13.3%) and recurrent nerve palsy in three patients (10%), but no in-hospital deaths were observed (Table III).

Table II. *Clinicopathological features after surgery (n=30).*

	n (%)
Pathological tumor depth	
T1a	6 (20%)
T1b	24 (80%)
Lymph node metastasis	
Positive	8 (27%)
Negative	22 (73%)
Pathological stage	
Stage IA	22 (73%)
Stage IIB	8 (27%)
Clinical outcomes	
Recurrence	2*(1.7%)
Cancer death	0

*Two patients had supraclavicular lymph node (LN) recurrence and underwent LN dissection followed by chemoradiotherapy.

Table III. *Postoperative complications after esophagectomy (n=30).*

	n (%)
Pulmonary complication	4 (13.3%)
Anastomotic leakage	5 (16.7%)
Recurrent nerve palsy	3 (10%)
Infection	1 (3.3%)
Mortality	0 (0%)

Clinical outcomes and late toxicities after chemoradiotherapy.

Two patients developed metachronous esophageal cancer and underwent ESD. One patient had cervical paraoesophageal lymph node recurrence and underwent lymph node dissection followed by CRT. There were no deaths from esophageal cancer, but there were nine deaths caused by other diseases, six of which were caused by other cancers (Table IV). In terms of late toxicity due to irradiation, grade 2 radiation pneumonitis and pleural effusion were observed in two patients each, grade 3 pericardial effusion was observed in six patients, and grade 4 pericardial effusion requiring pericardiocentesis was observed in one patient. Six patients had esophageal stricture of grade 2 or higher, and three of them had grade 3 stricture requiring dilatation after hospitalization for fluid supplementation due to difficulty in oral intake (Table V).

Prognosis. There were no esophageal cancer deaths in the surgery and CRT groups, and the disease-specific survival was 100% in both groups. Overall survival was significantly better in the surgery group, with 5-year survival rates of 92.6% and 81.0% in the surgery and CRT groups, respectively (Figure 1).

Table IV. *Clinical outcomes after chemoradiotherapy (n=37).*

	n
Metachronous esophageal cancer	2*
Recurrence	1**
Cancer death	0
Other disease death (Other cancer death)	9 (6)

*Two patients developed metachronous esophageal cancer and underwent endoscopic submucosal dissection. **One patient had cervical paraoesophageal lymph node (LN) recurrence and underwent LN dissection followed by chemoradiotherapy.

Table V. *Grade ≥ 2 late toxicities after chemoradiotherapy (n=37) (RTOG/EORTC late radiation morbidity scoring scheme).*

	Grade:number
Radiation pneumonitis	G2:2
Pleural effusion	G2:2
Pericardial effusion	G3:6; G4:1
Stenosis of esophagus	G2:3; G3:3

Discussion

In recent years, endoscopic resection of superficial carcinoma of the esophagus for the purpose of diagnosis has been widely performed in the absence of clinical evidence of lymph node and other-organ metastases. The greatest advantage of prior endoscopic resection is that the pathological diagnosis after resection can identify cases of intramucosal carcinoma without vascular invasion, and surgery can be avoided in these cases. In contrast, if the pathological examination after endoscopic resection reveals that the possibility of lymph node metastasis is high, a subtotal esophagectomy has been commonly performed.

In a recent parallel-group controlled trial of esophagectomy and CRT for superficial esophageal cancer with no clinical lymph node metastasis, CRT was reported to have a non-inferior overall survival to surgery (8). If the prognoses of surgical resection and CRT are equivalent for superficial esophageal cancer, then it can be assumed that CRT and surgery are also equally effective as additional treatment after endoscopic resection. Minashi *et al.* conducted a prospective large-scale clinical trial of endoscopic treatment followed by CRT for superficial esophageal cancer with clinically negative lymph nodes, and reported an excellent 3-year overall survival rate of 90.7% (9). Based on this favorable outcome, they concluded that selective CRT based on diagnostic ER might

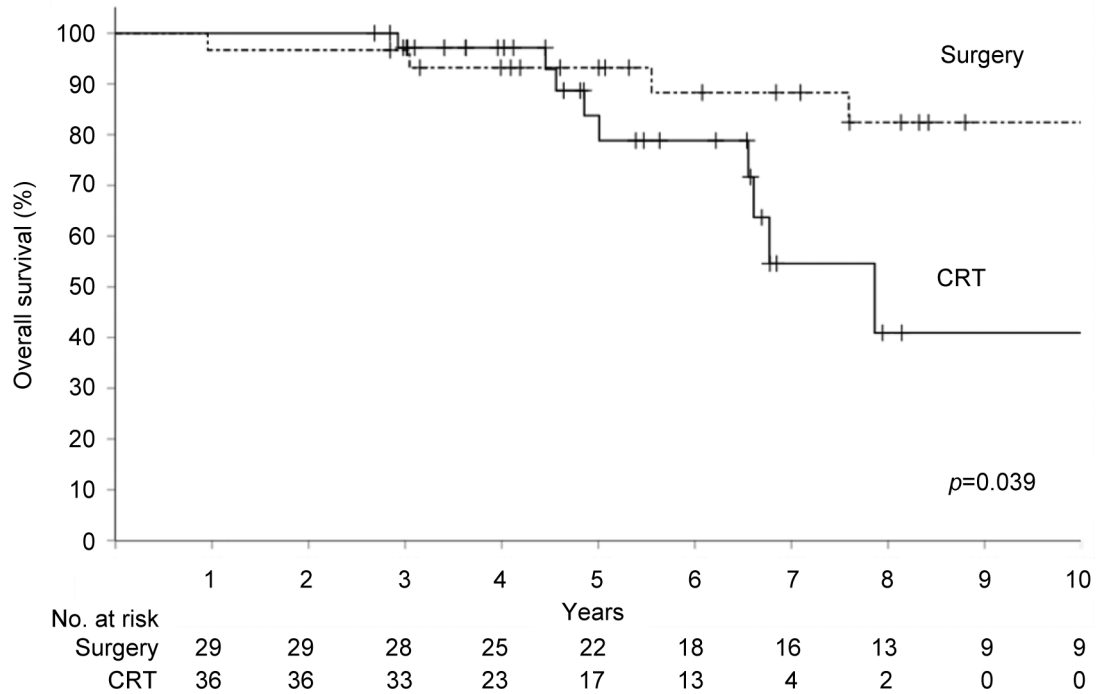


Figure 1. Overall survival of patients in the surgery group (dotted line) and the chemoradiotherapy (CRT) group (solid line).

be a standard treatment option for clinically suspected T1b (SM1-2) N0M0 esophageal squamous cell carcinoma as a minimally invasive approach.

In the present study, the 5-year survival rate of the CRT group was 81%, and there was no death from the primary disease. Patients who underwent resection as an additional treatment after endoscopic resection also had a very good 5-year survival rate of 92.6%. Since there were no deaths from the primary disease in either group, we believe the surgery group had a significantly better prognosis than the CRT group because of the higher number of deaths from other diseases in the CRT group. Patients who were considered inappropriate for surgery due to old age or concurrent other cancers were treated with CRT as an additional therapy, and this was thought to be the reason why there were more deaths from other diseases in the CRT group.

The greatest advantage of CRT over surgery is the ability to preserve organs, but preserving the esophagus brings with it the risk of developing heterogeneous esophageal cancer. However, in this study, only two cases of metachronous esophageal cancer developed after CRT therapy, and all cases were cured by endoscopic treatment.

In addition, esophageal stricture was observed as a late toxicity in a relatively high number of patients who underwent CRT after endoscopic treatment. It is important to avoid the development of persistent stenosis because it can significantly

reduce the quality of life. Mucosal resection of a tumor circumferential extent greater than 75% and a primary lesion in the cervical esophagus have been reported as risk factors for stricture after endoscopic treatment (10, 11). Furthermore, irradiation itself has been reported to be a factor causing stenosis after endoscopic resection, thus it is important to avoid irradiating patients with a high risk of such stenosis (12). Therefore, to avoid stricture, we suggest that patients with superficial carcinoma of the cervical esophagus, who are not considered candidates for surgery due to the difficulty in preserving the larynx, should be treated with radical CRT as the initial treatment instead of endoscopic resection. Similarly, in cases where the lesion is more than 3/4 circumferential and the depth of the lesion is suspected to be submucosal based on endoscopic imaging, we believe that surgery could be selected from the initial stage.

The limitations of this study are that it is a retrospective study, conducted at a single institution, and patients who were judged to be ineligible for additional treatment received CRT, therefore there is a bias in the patient background between the two groups.

In conclusion, surgery and CRT may be equivalent for additional treatment after endoscopic resection of superficial esophageal cancer with negative clinical lymph nodes. Except for patients with a high risk of stenosis or radiation-induced interstitial pneumonia, CRT was considered to be an adequate additional treatment in terms of organ preservation.

Conflicts of Interest

The Authors declare no competing interests in association with the present study.

Authors' Contributions

Conception and design: Manabu Emi and Morihito Okada. Contribution to patient care: Yuji Murakami, Ikuno Nishibuchi, Yasushi Nagata, Toru Yoshikawa, Ryosuke Hirohata and Manato Osawa. Collection and assembly of data: Manabu Emi and Yoichi Hamai. Data analysis and interpretation: Manabu Emi, Yoichi Hamai, and Yuji Murakami. Manuscript writing: Manabu Emi. Final approval of manuscript: All Authors.

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