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Combination Therapy After EMR/ESD for Esophageal Squamous Cell Carcinoma with Submucosal Invasion

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1. Introduction

Recently, nonoperative treatment such as chemotherapy or radiotherapy has commonly been performed for submucosal carcinoma of the esophagus. Although endoscopic mucosal resection¹⁾²⁾ (EMR) or endoscopic submucosal dissection³⁾ (ESD) is usually done as curative treatment for mucosal cancer of the esophagus, the efficacy of multimodal therapy combined with EMR/ESD for esophageal squamous cell carcinoma (SCC) with submucosal invasion is controversial.

At our hospital, several patients who had SCC with submucosal invasion received multimodal therapy combined with EMR or ESD, and the results are reported here.

2. Patients and methods

From 1996 to 2005, 36 patients who had esophageal SCC with submucosal invasion underwent multimodal treatment. Esophagectomy was not performed because of associated complications in 19 cases and due to patient refusal in 17 cases.

In all patients, EMR/ESD was performed before any other treatment. Then chemotherapy, radiotherapy, or chemoradiotherapy was added, depending on the histopathological findings, which were classified according to the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus⁴⁾. Submucosal invasion was classified into the following three grades: sm1: $\leq 200 \mu\text{m}$, sm2: $> 200 \mu\text{m}$, and sm2 EM (+): residual cancer cells at the resected margin.

In principle, radiotherapy or chemoradiotherapy was added if the resected margin was suspected to contain residual cancer cells, while chemotherapy was performed if lymphatic invasion was found in the resected specimen (Fig 1). Argon plasma coagulation was added without radiation if the residual tumor was limited to a small area.

2.1 Method of EMR

EMR was performed by the EEMR or EMRC method¹⁾²⁾. EMRC was done by using a single-channel endoscope (GIF Q260; Olympus) with a cap (Olympus, Tokyo, Japan). After chromoendoscopy with iodine solution, saline was injected into the submucosal layer.

Next, a snare (SD-7P, Olympus) was opened inside the cap, the tumor was aspirated into the cap, and the snare was closed. The forced coagulation mode was used to perform resection. EMMR was done by using a single-channel endoscope (GIF Q260; Olympus) fitted with an EEMR-tube. The method was same as that for EMRC until the injection of saline. Then a snare (SD-7P, Olympus) was passed through a side channel of the tube and was opened over the tumor. The tumor was aspirated into the tube using the suction of the endoscope and the snare was tightened. Resection was done in the forced coagulation mode.

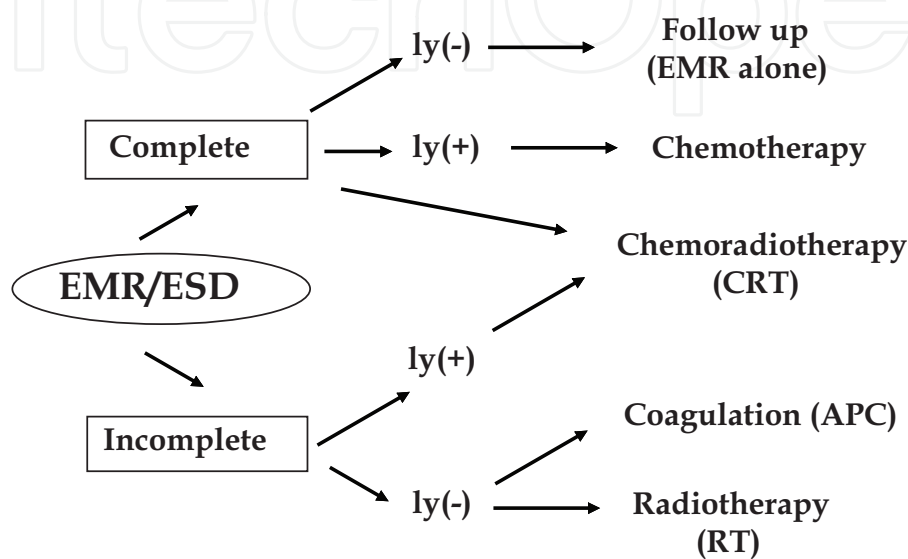


Fig. 1. Fundamental clinical course

2.2 Method of ESD

A hook knife from Olympus (Tokyo, Japan) was used for the hook knife method of ESD³⁾⁵⁾ along with a single-channel endoscope (GIF Q260; Olympus) and an attachment. The electrical generator was a VIO (ERBE, Tübingen, Germany). Before marking, chromoendoscopy with iodine solution was done to identify the lateral margins of the lesion. Then marking was undertaken in the hook knife using the forced coagulation mode. After 10% glycerin was injected into the submucosal, mucosal incision was performed in the endo cut mode. Before performing submucosal dissection, hyaluronic acid solution was injected into the submucosal lesion. Then the clip with thread was attached to the oral border of the specimen and the thread was pulled in the oral direction to exert traction on the submucosal layer. Next, the submucosal lesion was dissected off the muscle layer by using the hook knife in the endo cut mode. Bleeding was controlled with hemostatic forceps (FD-411QR; Olympus) in the soft coagulation mode or with the hook knife in the spray mode. ESD was performed with the patient under sedation by intravenous administration of diazepam and pentazocine as required plus continuous infusion of propofol.

2.3 Chemotherapy and radiotherapy

Chemotherapy was performed for 2 courses if lymphatic invasion was found in the resected specimen. Patients were principally given a combination of cisplatin/5-fluorouracil or nedaplatin/5-fluorouracil (Fig. 2). Radiotherapy was given to a total dose of 50-60 Gy, with the radiation field being limited to the local tumor area (Fig. 3).

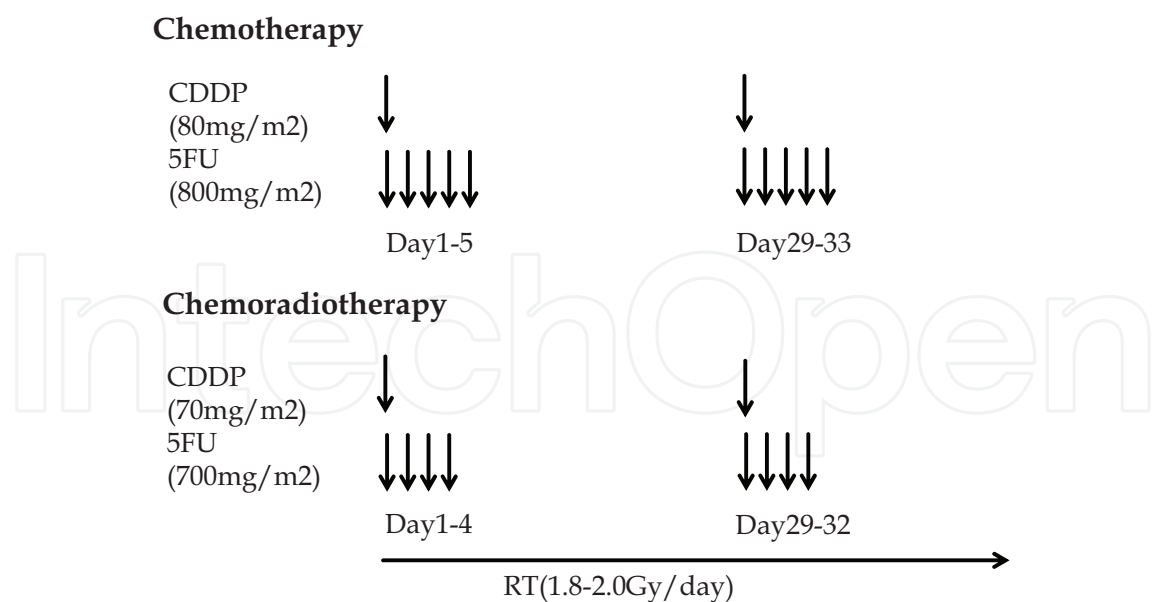


Fig. 2. Chemotherapy and chemoradiotherapy

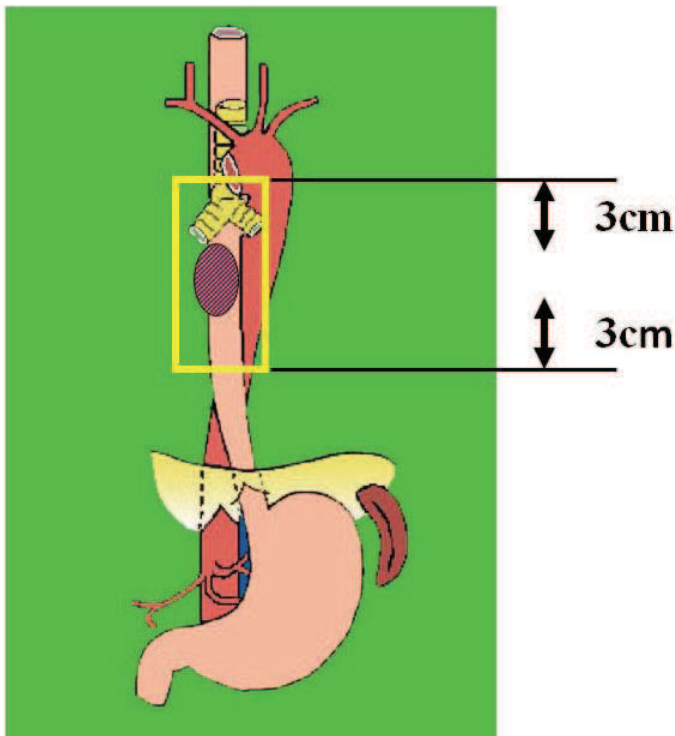


Fig. 3. The radiation field was limited to local area

3. Results

There were no complications of EMR/ESD. On histopathological examination, the depth of tumor invasion was sm1 in 22 cases, sm2 in 9, and sm2 EM (+) in 5. Lymphatic invasion (ly) was found in 18 cases (50%), and there was 1 case (3%) of vascular invasion (v). Sixteen patients were treated with EMR alone, 8 received EMR + chemotherapy, 2 had EMR + radiotherapy, and 10 had EMR + chemoradiotherapy.

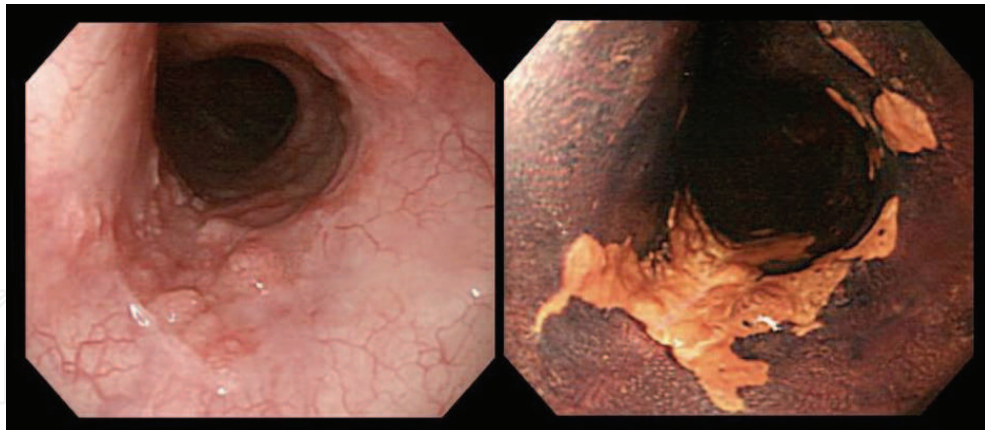
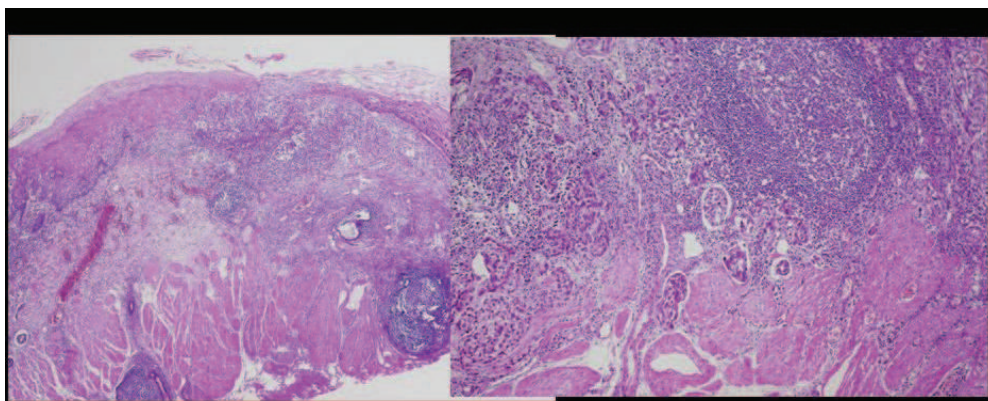


Fig. 4. 0-IIa+IIc lesion was seen in middle esophagus. EMR was performed



Mod.SCC,pSM1, ly3, v0, INFc→CRT(ND+5FU, 66Gy)

Fig. 5. Though pathological finding showed moderate. SCC, pSM1, ly3, v0, chemoradiotherapy was treated

Recurrence was diagnosed in three patients. Medistinal lymph node recurrence occurred in a man with moderately differentiated SCC (sm1, ly (-)) treated by EMR alone and cervical lymph node recurrence was detected in 1 woman with moderately differentiated SCC (sm2, ly (+)) treated by EMR alone. Both cervical lymph node recurrence and intramural metastasis were detected in 1 man with moderately differentiated SCC (sm1, ly (+)) treated by EMR + chemoradiotherapy (Fig. 4-6). Local recurrence did not occur.

There was 1 death from the primary disease and 10 patients died of other diseases. The overall survival rate was 69% (Fig. 7).

4. Discussion

Curative surgery has been considered the standard treatment for squamous cell carcinoma of the esophagus with submucosal invasion (T1b) because of the possibility of lymph node metastasis⁽⁶⁾⁽⁷⁾⁽⁸⁾. Although chemoradiotherapy (CRT) has been performed recently for T1bN0 cancer, it is controversial whether CRT has the same therapeutic effect as surgery, and a randomized controlled trial of surgery versus CRT is still ongoing.

EMR has become widely employed for esophageal early carcinoma⁽¹⁾⁽²⁾ at a large number of institutions⁽¹⁰⁾. ESD has been adopted for the treatment of early esophageal cancer as a

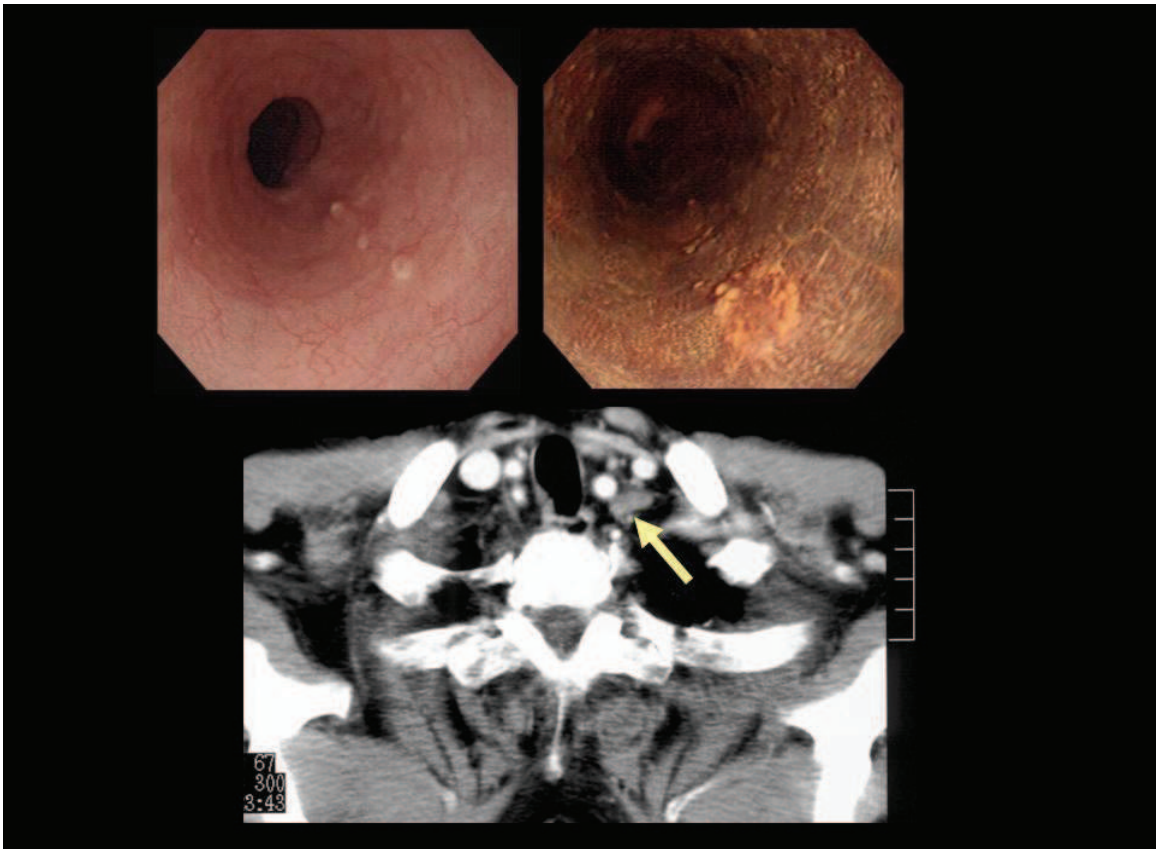


Fig. 6. After 6 month later, intramural metastasia and cervical lymph node were detected. The patient died from the primary disease

method of excising extensive lesions en bloc. Endoscopic resection was previously considered to be curative for tumors limited to the proper mucosal layer⁹⁾. Although the indications of EMR/ESD have been extended to tumors with invasion of the muscularis mucosae and submucosal tumors with a comparatively low rate of lymph node metastasis in recent years¹¹⁾⁻¹³⁾, these procedures are not indicated for tumors invading deeply into the submucosal layer.

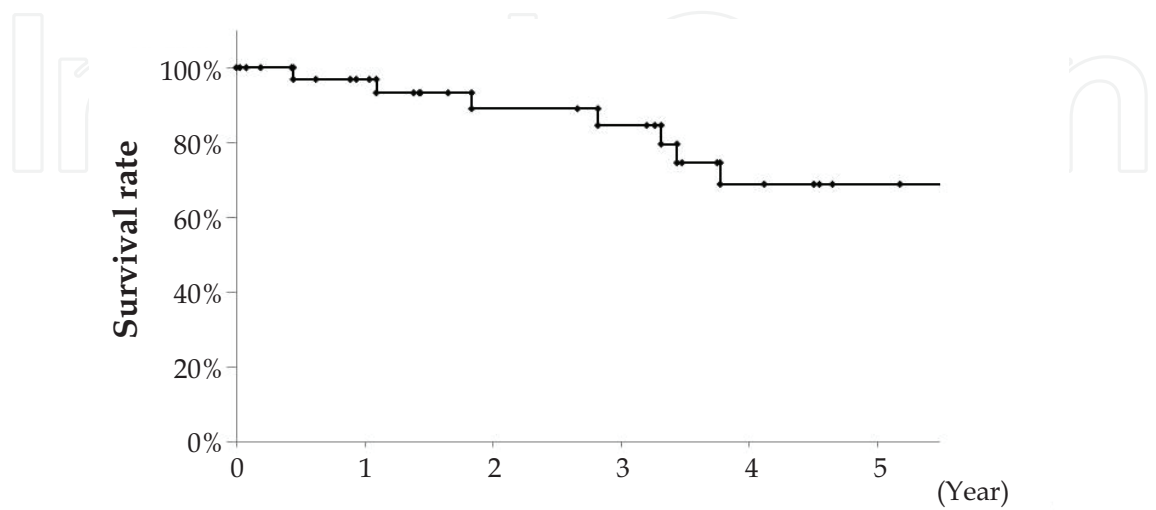
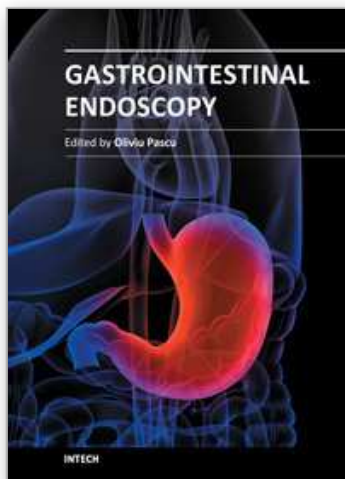


Fig. 7. Over all survival

One advantage of EMR/ESD is that histopathological examination is possible, which allows us to identify the patients who do not need chemotherapy or radiotherapy. EMR/ESD seemed to be effective because there was no local recurrence and residual tumor. There were many high risk patients in our series, so deaths from other causes were frequent. Thus, a randomized controlled trial will be needed to evaluate the correct survival rate. There were also cases of cervical and mediastinal lymph node recurrence in our series. These lymph nodes are removed by esophagectomy with 3-field dissection, so recurrences would have been avoided if esophagectomy had been performed in such patients. Accordingly, EMR/ESD needs to be selected carefully.

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Endoscopy has had a major impact in the development of modern gastroenterology. By using different data it provided a better understanding of pathogenic mechanisms, described new entities and changed diagnostic and therapeutic strategies. Meanwhile, taking advantage of many technical advances, endoscopy has had a developed spectacularly. Video-endoscopes, magnification, confocal and narrow-band imaging endoscopes, endoscopic ultrasounds and enteroscopes emerged. Moreover, endoscopy has surpassed its function as an examination tool and it became a rapid and efficient therapeutic tool of low invasiveness. InTech Open Access Publisher selected several known names from all continents and countries with different levels of development. Multiple specific points of view, with respect to different origins of the authors were presented together with various topics regarding diagnostic or therapeutic endoscopy. This book represents a valuable tool for formation and continuous medical education in endoscopy considering the performances or technical possibilities in different parts of the world.

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