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Retrospective Study

Endoscopic debulking resection with additive chemoradiotherapy: Optimal management of advanced inoperable esophageal squamous cell carcinoma

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Abstract

BACKGROUND

There is no remedial strategy other than definitive chemoradiotherapy (dCRT) for patients with advanced esophageal squamous cell carcinoma (ESCC) who are not eligible to undergo surgical treatment.

AIM

To introduce a novel therapy called endoscopic debulking resection (EdR) followed by additive chemoradiotherapy (CRT) and evaluate its efficacy and safety.

METHODS

Advanced inoperable ESCC patients between 1 January 2015 and 30 December 2019 were investigated retrospectively. Patients who received EdR followed by CRT were deemed the EdR+CRT group, and those without CRT were deemed the EdR group. Overall survival (OS), progression-free survival (PFS) and adverse events (AEs) were evaluated.

RESULTS

A total of 41 patients were enrolled. At a median follow-up of 36 mo (range, 1-83), the estimated 1-, 2-, and 3-year cumulative OS rates of patients who underwent EdR plus additive CRT were 92.6%, 85.2% and 79.5%, respectively, which were higher than those of patients who underwent EdR alone (1-year OS, 83.3%; 2-year OS, 58.3%; 3-year OS, 50%; $P = 0.05$). The estimated 2-year cumulative PFS rate after EdR+CRT was 85.7%, while it was 61.5% after EdR ($P = 0.043$). According to the univariate and multivariate Cox regression analyses, early clinical stage (stage \leq IIB) and additive CRT were potential protective factors for cumulative OS. No severe adverse events were observed during the EdR procedure, and only mild to moderate myelosuppression and radiation pneumonia were observed in patients who underwent additive CRT after EdR.

CONCLUSION

EdR plus CRT is an alternative strategy for selected advanced inoperable ESCC patients.

Key Words: esophageal squamous cell carcinoma; endoscopic resection; chemoradiotherapy; overall survival; progression-free survival

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Core Tip: Forty-one advanced ESCC patients were retrospectively enrolled; 28 patients underwent endoscopic debulking resection (EdR) plus chemoradiotherapy (CRT), while 13 received EdR without CRT. Clinicopathological characteristics, perioperative outcomes, cumulative OS and PFS rates were analyzed. Our results confirm that EdR is safe and feasible for advanced ESCC patients and that EdR+CRT showed better OS and PFS than EdR alone.

INTRODUCTION

Esophageal carcinoma (EC) is the sixth leading cause of cancer-related death worldwide [1]. The incidence of esophageal squamous cell carcinoma (ESCC), the main type of EC in China, ranks sixth, while its mortality ranks fourth [2]. Over the past decades, clinicians have made great efforts to improve the therapeutic outcomes of ESCC. Early ESCC with stage T1a (mucosal invasion) can be completely cured by endoscopic resection (ER), including endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) [3]. With regard to T1b (submucosal invasion), studies have reported moderate rates of metastasis in SM1 and high rates of metastatic lymph nodes in SM2 and SM3. For those patients with deeper than SM2 invasion or who undergo noncurative ER (R1 resection), additional treatments such as esophagectomy are always recommended.

Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is currently recommended as the standard therapy for advanced ESCC [4-6]. Advanced ESCC patients who decline to receive surgical treatment or have high surgical risks must choose definitive CRT (dCRT) [7-9]. However, locoregional failure of dCRT is usually unavoidable [10, 11]. Patients undergoing dCRT who develop recurrent cancer often have a poor prognosis, with a reported median survival of 4 to 28 mo [11]. A series of studies have reported that salvage ER is a promising strategy for locally recurrent lesions after dCRT [12-15], which is good news for recurrent patients. However, salvage ER was deemed to be applicable to superficial lesions only. Furthermore, radiation-induced fibrosis in the submucosa increases the incidence of perforation and bleeding during ER. Therefore, novel strategies that are minimally invasive for advanced inoperable ESCC are urgently needed.

A single-arm prospective study reported by Minashi K *et al* concluded that the combination of ER and selective CRT was comparable to surgery, being regarded as a minimally invasive therapy for T1b(SM1-2)N0M0 patients [16]. Subsequent studies also showed that ER plus CRT had equivalent OS potential to that of esophagectomy for

early ESCC patients [16-18], further confirming its high therapeutic value for noncurative ER. However, there are no reports on whether ER plus CRT is suitable for patients with deeper than SM3 invasion.

In this study, we used a new therapy called endoscopic debulking resection (EdR) to treat selected patients diagnosed with advanced ESCC who were unable to undergo surgery, and we extended this treatment option to patients with deeper than T1b (\geq SM3) invasion who were unwilling to receive additional esophagectomy in an attempt to evaluate its efficacy and safety when performed along with additive CRT.

MATERIALS AND METHODS

Patients

From 1 January 2015 to 30 December 2019, patients diagnosed with clinical stage T1b (SM3)-T4N0/+M0/+ inoperable ESCC in our institution were retrospectively included. The inclusion criteria of patients who underwent EdR were as follows: 1) protruding tumor growth; 2) tumor invasion \geq SM3; and 3) cervical inoperable ESCC or unwillingness to or unable to receive esophagectomy. Patients who had other concurrent malignancies and needed extra therapies were excluded. Patients who received EdR in our study were all suggested to undergo additional selective CRT. The choice of different CRT strategies was made based on the pathological diagnosis and the patients' physical tolerance.

All patients were staged with 18 fluorodeoxyglucose positron emission tomography combined with computed tomography (18 FDG-PET/CT) or computed tomography (CT). Magnification endoscopy (ME) and endoscopic ultrasound (EUS) were used to assess the T- and N-stage of each patient. The grading of tumors was performed according to the 2010 WHO classification of tumors of the digestive system. The TNM stage of the tumor was determined according to the American Joint Commission on Cancer (AJCC) and Union of International Cancer Control 8th (UICC).

Debulking resection procedure

EdR was performed by experienced endoscopists in our center (**Fig. 1**). All patients underwent operation under intubation anesthesia. Carbon dioxide insufflation and a GIF-H260 endoscope (Olympus, Tokyo, Japan) fitted with a transparent cap (Tokyo, Japan) were used during the therapy. We handled a VIO-300D electrosurgical generator (ERBE, Tübingen, Germany), set to Endocut I mode, with Effect 2 for incision and coagulation and Effect 3 (40 W) for dissection. The lesion border was marked by making spots around it with a Hybrid Knife (ERBE, Tübingen, Germany). A mixture of saline solution diluted with methylthionine chloride and epinephrine was injected into the fundus of the lesion. Sometimes, hyaluronic acid is used for its efficiency and persistency. However, as the lesion in our study always deep in submucosa, it was difficult to create submucosal fluid cushion and lift the lesion completely. In this case, we did the separation along the stripping imaginary line and dissected lesions carefully step by step. The tumor was removed with a snare by fragment resection. Bleeding vessels were coagulated by hemostatic forceps (FD-410LR, Olympus, Japan). A fully covered esophageal stent (Micro-Tech Co., Ltd., Nanjing, China) was chosen depending on the postoperative wound, which was resected to the muscularis propria. After the operation, all patients fasted for at least 24 h and were treated with acid suppression, hemostasis and anti-infection agents. The specimens were examined by experienced pathologists who referred to the Japanese Classification of Esophageal Cancer, 11th edition.

Chemoradiotherapy

Radiotherapy was administered 2 mo after EdR. A megavoltage photon beam (16-18 MV), a computed tomography (CT) simulator and a radiation treatment planning system were used at our institution. Tumor bed volume (GTVtb) was defined as the volume of the primary tumor. GTVtb was expanded to the planning target volume (PGTVtb) by extending 1 cm in all three dimensions. The clinical tumor volume (CTV) included the tumor bed and some optional areas of the regional lymph nodes (bilateral supraclavicular, periesophageal, mediastinal and perigastric). The planning target volume (PTV) included the CTV plus a margin of 0.5 cm. Three-dimensional

radiotherapy treatment planning was performed to reduce the dose to the normal organs. A total dose of 40 to 46 Gy in 20 fractions was delivered with intensity-modulated radiotherapy or anterior/posterior opposed portals according to the normal organs. A tumor boost of 4-6 Gy was delivered to the tumor bed after EdR. All patients were treated 5 days a week.

Based on the patient's physical state, different chemotherapy regimens were administered based on the pathological diagnosis and the patient's physical condition. The chemotherapy regimens in our study comprised (1) cisplatin plus 5-fluorouracil (5-FU): two cycles of cisplatin (70 mg/m²/d) on Day 1 and 5-FU (700 mg/m²/d) on Days 1-4 at an interval of 4 wk; (2) nedaplatin plus 5-FU: the dosage and administration schedule were the same as those for cisplatin plus 5-FU; (3) docetaxel plus 5-FU: docetaxel (7.5 mg/m²/d, Days 1, 8, 22, and 29) and continuous infusion of 5-FU (250 mg/m²) on Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40 and 43-45 (Table S1).

Follow-up

Patients were monitored with weekly hematological examinations, including blood cell counts, liver and kidney function tests, tumor marker tests, electrocardiography, esophagogastroduodenoscopy (EGD), and neck-to-abdominal CT every 3 mo. Local recurrence and metastatic recurrence were defined as a positive biopsy at endoscopy, metastatic lesions to distant organs and/or local lymph nodes enlarged inside of the irradiation area on ¹⁸FDG-PET/CT or CT. The follow-up cutoff date was 31 December 2021.

Outcomes

The primary end point was overall survival (OS), defined as the time from the date of the initial treatment to the date of death from any cause or the date of the last contact. The key secondary end point was progression-free survival (PFS), which was measured as the time from treatment to either progression or death from any cause or the date of the last follow-up. Other secondary endpoints were AEs of treatments, according to the National Cancer Institute Common Terminology Criteria (NCI-CTCAE ver. 4.0).

Statistical analysis

Categorical data were compared between groups by Fisher's exact test or the chi-square test; for quantitative data with a nonnormal distribution, the nonparametric Mann-Whitney U test was used. Quantitative data are expressed as mean \pm standard deviation or median (range). Kaplan-Meier survival analysis was performed using SPSS 26.0 statistical software (IBM, New York, USA). Univariate and multivariate analyses using the Cox proportional hazards regression model were run to evaluate the influence of covariates on OS and PFS. $P < 0.05$ was considered to indicate significance.

RESULTS

Baseline characteristics

A total of 41 eligible patients were included retrospectively, the study flow diagram is shown in Figure 2. Among them, 12 patients had a high surgical risk of esophagectomy, 10 patients suffered proximal esophageal carcinoma, 13 patients were unwilling to receive esophagectomy, and the other 6 patients were unable to undergo esophagectomy due to a previous surgical history ($n = 1$, massive small intestine resection; $n = 1$, lung cancer resection; $n = 2$, gastric cancer resection; $n = 2$, cardia cancer resection). Twenty-eight patients underwent EdR plus CRT (EdR+CRT group), while 13 received EdR without CRT (EdR group). Among the 13 patients in the EdR group, 2 preferred not to undergo CRT due to poor physical condition, 9 due to older age (>70 years), and 2 due to complications with fistulas.

The median age of the 41 enrolled patients was 69 years (range, 38-91). The median follow-up period was 36 mo (range, 1-83). Among the 41 cases, there were 22 (54%) primary tumors located less than 25 cm from the incisors, while 19 (46%) were located more than 25 cm from the incisors. There were 17 (42%), 23 (56%) and 1 (2%) patients diagnosed with clinical stage T1b-SM3, T2, and T3 disease, respectively. Seven (17%) patients had lymph node metastases, while 2 (5%) patients had M1 metastases. The clinical characteristics of the enrolled patients are listed in Table 1. There were no significant differences in the baseline clinical characteristics between the two groups.

Outcomes and AEs of EdR and CRT

The EdR was performed successfully in all 41 patients (**Table 2**). Ten (24%) received R0 resection, while 31 (76%) patients received R1 resection (deemed positive horizontal/vertical margins or unjudged margins). The procedure time, measured from the start of marking the lesions to the end of treatment, was 65 ± 29 min (range, 25-150 min). No intraoperative adverse events were observed, except for one (1/41) case of mild subcutaneous emphysema, whose symptoms were relieved after 2 days of conservative treatment. Two patients (2/41) suffered delayed bleeding 7 days after the procedure but recovered with anti-acid therapy. Two patients (2/41) developed esophagotracheal fistula within 2 mo after EdR, of which one died at 24 mo, and the other was lost to follow-up at 25 mo. A total of 19 patients (19/41) developed degrees of esophageal stenosis: 2 patients were lost to follow-up at 25 mo and 30 mo, 16 had alleviated dysphagia after receiving retrievable stenting or bougie dilation, and 1 died due to esophagotracheal fistula at 24 mo.

After EdR, 28 patients received additive CRT. Complications such as myelosuppression were observed in 7 patients, including 5 cases of Grade I, 1 of Grade II, and 1 of Grade III. Three patients developed Grade I radiation pneumonia, and 3 patients suffered Grade II mucous toxicity. No severe adverse events were observed during the CRT procedure.

Survival outcomes

The median follow-up period was 36 (1-83) months, and 2 patients were lost to follow-up at 25 mo and 30 mo. The estimated 1-, 2-, and 3-year cumulative OS rates of the EdR+CRT group were 92.6%, 85.2% and 79.5%, respectively, which were higher than those of the EdR group (1-year OS, 83.3%; 2-year OS, 58.3%; 3-year OS, 50%; $P = 0.05$) (**Fig. 3A**). As shown in **Fig. 3B**, the estimated 2-year PFS ²rate of the EdR+CRT group was 85.7%, higher than that of the EdR group (61.5%, $P = 0.043$). Univariate Cox regression analyses showed that clinical stage, additive CRT, lymphoid metastasis and distant metastasis were potential influencing factors of cumulative OS. These variables were included in a multivariate Cox regression analysis, which identified clinical stage as the only factor affecting OS. Similarly, early clinical stage and no lymphoid or distant

metastasis were independent protective prognostic indicators for PFS in univariate Cox analyses, but multivariate analysis found only early clinical stage as a protective factor associated with PFS (**Table 3**).

DISCUSSION

Patients who undergo noncurative R1 resection or have deeper than SM2 invasion always need additional esophagectomy. However, this concept faced challenges due to the possibility of no residual tumor present in the surgical specimen. Furthermore, esophagectomy is not a sensible choice for patients who are at high risk from surgery. For advanced ESCC, patients who suffer from cervical or upper esophageal cancer and have a history of lower esophageal or cardiac surgery usually miss the opportunity for esophagectomy. Here, we tested a new treatment, endoscopic debulking resection (EdR), on selected inoperable advanced ESCCs and extended it to patients with SM3 invasion who were unwilling to receive additional esophagectomy. The results revealed an encouraging short-term OS and low AE rate. Patients who received additive CRT after EdR had a better survival prognosis than those who received only EdR.

ER is relatively indicated for submucosal lesions, especially SM1-2 invasion. It is not recommended to perform ER for SM3 invasion because of the higher metastasis risk. The literature is unclear regarding additional esophagectomy following noncurative ER. As ER can obtain accurate T staging while remove the primary lesion, adjuvant CRT therapy can further reduce the potential of metastasis or recurrence, ER plus CRT is considered to be an alternative strategy of esophagectomy for clinical stage I ESCC [19-21]. Followed studies also showed that ER followed by CRT displayed comparable outcomes of esophagectomy for T1b (SM1-2) cancer [22]. However, it is unclear whether ER followed by CRT is applicable to SM3 invasion. Here, we tentatively performed ER plus CRT in patients with SM3 invasion. Among the 41 patients, 17 patients had T1b-SM3 cancer, and 5 out of 17 patients underwent R1 resection. Five patients with R1 resection received additional CRT, except 1 due to a history of severe emphysema. For these 17 patients, follow-up lasted 24 to 83 mo, and a favorable prognosis was found,

except for 1 failed follow-up at 30 mo post-ER. It is worth noting that 4 patients in our hospital with SM3 invasion who underwent R1 resection plus supplemental esophagectomy showed negative residual tumors and negative nodal metastases in the surgical specimens. Whether additional surgery or additive CRT be adopted for patients with lesions deeper than SM3 requires large prospective studies.

For advanced inoperable ESCC, dCRT is the only choice. Previous studies reported the 5-year OS of ESCC patients who received dCRT was only 20-27%, with a median survival of 14 mo [23, 24]. Furthermore, the incidence of local failure of dCRT was up to nearly 50%, with poor life quality [25]. Another randomized phase III trial enrolled 267 unresectable ESCC patients received dCRT showed a median PFS was merely 9.7 mo [26]. There is an urgent need for a new strategy that is more effective than dCRT for unresectable ESCCs. Salvage ER, a complementary treatment after dCRT, has exhibited decent results in recent studies. Yano *et al* showed that the 5-year survival rate of salvage EMR of stage I-III esophageal cancer patients after dCRT was 49.1% [13]. Another retrospective study, reported by Nakajo *et al*, concluded that the 1-year local relapse-free survival (LRFS) rates of salvage ESD were 86% - 100% [25], confirming the role of salvage ER in patients with dCRT failure [25, 27, 28]. Nevertheless, these patients all had localized and superficial lesions with no lymph node or distant metastasis. In addition, radiation-induced fibrosis and vessel vulnerability lead to a high risk of acute AEs such as bleeding or perforation.

In this study, we enrolled 41 patients, including 17 with T1b tumors, 23 with T2 and 1 with T3. Seven (17%) patients had lymph node metastases, while 2 (5%) patients had M1 metastases. The primary tumor was partially or completely removed from all enrolled 41 patients, with a mean procedure time of 65 ± 29 min. Only two patients suffered delayed bleeding, and one suffered mild subcutaneous emphysema, with no severe intra- or postoperative AEs observed. All of them were cured by conservative therapy. It is recognized that lesions with a circumferential extension of $> 3/4$, depth of invasion above M2, and mucosal defects longer than 3 cm are independent risk factors for esophageal stricture [29, 30]. Since the lesions in our study were mostly deeper than

SM2 and muscularis propria injuries, esophageal stents were implanted intraoperatively in 15 patients (15/41) to prevent postoperative stricture and delayed bleeding or perforation. Reassuringly, 7 of the 15 patients have no esophageal stenosis during follow-up, while the remaining 8 intake semi-fluid smoothly. It is well known that esophageal stenosis usually occurred late in the radiotherapy. Once the radiation esophagitis and stenosis occurred, the bleeding or perforation risks of endoscopic therapy were extremely high. Although the complication of stenosis in our study was 46% (19/41), it was manageable as all of them intake semi-fluid smoothly. In spite of this, patients who have a high risk of stenosis choose EdR should fully understand and accept this likely complication. Clinicians must also be cautious when choosing EdR for those with high stricture risk.

Patients who receive dCRT always suffer complications such as hemorrhage, perforation, radiation esophagitis, pericarditis, pneumonia, and tracheal stenosis. The fatal complication of tracheoesophageal fistula occasionally occurred, especially under the conditions of a high RT dose [31, 32]. One study reported that 6 of 49 patients (12%) with T1 or T2 esophageal cancer developed tracheoesophageal fistula, and 3 of them died. A list of studies reporting the rates of esophageal fistula in locally advanced ESCC patients who received dCRT varied from 3.7% to 24%. In our study, there were no fistulas in the EdR + CRT group, while 2 patients suffered fistulas in the single EdR group. We think that incomplete tumor resection and stent mechanical compression were the main reasons for the fistulas. Patients suffering from fistulas always have a poor prognosis due to the severe infection and malnutrition. We usually plant a fully covered esophageal stent to plug the fistula, but as a residual necrotic tumor, the fistula cannot be completely cured. To our delight, patients who received EdR plus CRT had no fistula up to our last follow-up. Our clinical experience tells us that the time point of additive CRT after EdR is extremely important. We implemented CRT at 2 mo after EdR, leaving sufficient time for esophageal mucosa repair. Furthermore, we reduced the ordinary radiation dose and reduced the scope of radiation treatment, relieving the toxicity of radiation. There were no severe adverse events in the EdR+CRT group.

Complications including mild myelosuppression, radiation pneumonia and mucous toxicity were observed in 25%, 11% and 11% of patients, respectively.

One study reported that the 5-year relative survival rate of ESCC patients treated with surgery is only 19%-24% [33]. Zhang *et al* showed that the 5-year OS of advanced ESCC patients who received adjuvant radiotherapy after surgery was 62.2%, which was much higher than the 5-year OS of patients who underwent surgery alone [34]. The survival benefit of postoperative chemotherapy has also been confirmed [35]. A randomized phase II trial reported by Liu S *et al* reported that ²the 3-year OS rate of advanced ESCC patients in the CRT group was 38.1%, while that in the induction chemotherapy group was 41.8% [36]. Other cohort studies that included stage II-III ESCC patients reported a median DFS of 13 mo in the CRT group [37] and a median OS in the CRT group of 14.1 mo [38]. In our study, the estimated 1-, 2-, and 3-year cumulative OS rates after EdR+CRT were 92.6%, 85.2% and 79.5%, respectively, and the estimated 2-year PFS rate after EdR+CRT was 85.7%, both satisfactory outcomes. The median survival time of the EdR+CRT group from Kaplan-Meier survival analysis was 76 mo. It is encouraging that 13 patients who received EdR alone also had fair outcomes, with a calculated median survival time of 26 mo. Although the number of EdR was small, the cumulative OS and PFS still were relatively good. According to univariate and multivariate Cox regression analyses, early clinical stage (stage \leq IIB) and additive CRT after EdR were potential protective factors.

The initial aim of our study was to remove the primary lesion, reduce tumor burden, and enhance the effect of CRT. This strategy was only a daring attempt, and the conclusions in our study need to be treated with caution. As mentioned above, our study has several limitations. First, this was a small, retrospective, short-follow-up study. It is clinically preferable to evaluate the 5-year OS, but ³we deemed it important to obtain results as soon as possible, so we ultimately designated the primary endpoint as the 3-year OS. Due to the special and strict eligibility criteria of patients, the number of patients in our study was small. Second, the study was conducted at a single institution,

which may limit its external generalizability. Large, multicenter, long-term follow-up studies are needed to validate the endoscopic advantages.

¹ Given the limitations above, the results should be interpreted with caution. However, to the best of our knowledge, this is the first study to expand the ER indicator of lesions deeper than SM3, and it is the first study to provide evidence regarding the efficacy and safety of EdR followed by CRT for advanced inoperable ESCC, which might become an attractive therapeutic strategy for selected ESCC patients.

CONCLUSION

EdR is an alternative strategy for selected advanced inoperable ESCC patients. Additive CRT was not associated with more adverse events but showed better prognosis than EdR alone.

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