Clinical Investigation

Multicenter Phase 2 Study of Cisplatin and 5-Fluorouracil With Concurrent Radiation Therapy as an Organ Preservation Approach in Patients With Squamous Cell Carcinoma of the Cervical Esophagus

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Received May 13, 2016, and in revised form Aug 23, 2016. Accepted for publication Aug 26, 2016.

Summary

This multicenter, phase 2 study is the first prospective study that showed chemo-radiotherapy (5-FU/CDDP/RT) for cervical esophageal cancer has sufficient efficacy.

Purpose: To clarify, in a multicenter, single-arm, phase 2 study (UMIN Clinical Trials Registry no. UMIN000001439), the clinical profile of chemoradiotherapy (CRT) for cervical esophageal cancer.

Patients and Methods: Patients with operable cervical esophageal cancer, excluding candidates for endoscopic resection, were enrolled. Protocol treatment consisted of CRT and adjuvant chemotherapy (CT). First, patients received concurrent CRT with 5-fluorouracil (5-FU) plus cisplatin (CDDP). Chemotherapy consisted of 5-FU at

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http://dx.doi.org/10.1016/j.ijrobp.2016.08.045

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700 mg/m² intravenous on days 1 to 4 and CDDP at 70 mg/m² intravenous on day 1, repeated every 4 weeks for 2 cycles. Radiation therapy consisted of 60 Gy in 30 fractions. After completion of CRT, 2 additional cycles of CT with 5-FU (800 mg/m², days 1-5) and CDDP (80 mg/m², day 1) were repeated at a 4-week interval. The primary endpoint was 3-year overall survival.

Results: Thirty patients were enrolled across 8 institutions in Japan, consisting of 26 men and 4 women with a median age of 64.5 years (range, 50-75 years). No grade 4 hematologic toxicity was seen in the CRT phase, and 1 grade 4 thrombocytopenia was seen in the CT phase. Grade 3 nonhematologic acute toxicities in the CRT phase were nausea (10%), mucositis (13.3%), and dysphagia (13.3%). No treatment-related death in either phase occurred. Overall complete response rate was 73%, and 3-year overall and laryngectomy-free survival were 66.5% and 52.5%, respectively. Regarding T4 disease, 3-year overall and laryngectomy-free survival were 58.3% and 38.5%, respectively.

Conclusions: This study, the first prospective study for cervical esophageal cancer, showed that CRT has sufficient efficacy and safety for use as an alternative to surgery for these patients.

Introduction

Cervical esophageal cancer is a rare disease that accounts for only 2% to 10% of all cases of esophageal cancer (1, 2). Previous prospective studies of esophageal cancer excluded (3-6) or enrolled only a few patients with cervical esophageal cancer (7). For this reason, reliable information on the clinical profile of chemoradiotherapy (CRT) for cervical esophageal cancer is scarce. In general, although high-quality evidence supports a recommended radiation therapy dose for tumors of the thoracic esophagus of 50 to 50.4 Gy, higher doses (>60 Gy) for tumors of the cervical esophagus may be acceptable (8), albeit evidence for this was not prospective. Several reports have described CRT for cervical esophageal cancer (9-12), but these were all retrospective analyses, and treatment regimens or planned radiation doses and methods have not been unified.

Moreover, hypopharyngeal cancer and cervical esophageal cancer are often treated by the same surgical approach (ie, total pharyngo-laryngo-esophagectomy) (2, 13-17), and only a few studies have focused exclusively on cervical esophageal cancer (18, 19). As a result, a standard, evidence-based approach to squamous cell carcinoma of the cervical esophagus has yet to be developed.

Here, we conducted a prospective study to clarify the clinical profile of CRT for pure cervical esophageal cancer.

The regimens used in this study were carefully discussed before the study was started.

With regard to radiation oncology, because the prophylactic irradiation field for cervical esophageal cancer differs from the thoracic esophagus, which includes the heart and lung, we considered that irradiation of >60 Gy would be safe. On the other hand, the risk of stenosis of the esophagus as a late toxicity with 70-Gy irradiation, the standard dose in head and neck cancer, seemed problematic. Accordingly, we established 60 Gy as an optimal irradiation dose.

From a medical oncology standpoint, cisplatin (CDDP) with concurrent radiation therapy is the gold standard in head and neck cancer, and platinum-based regimens are also accepted.

In contrast, 5-fluorouracil (5-FU)-based regimens seem to be standard in esophageal cancer.

The larynx, which is included within the irradiation area, is more susceptible to severe mucositis induced by 5-FU and radiation therapy than the thoracic esophagus.

Accordingly, we determined that the amount of 5-FU should be set lower than that in the Radiation Therapy Oncology Group protocol 85-01.

Patients and Methods

This study was conducted under a multicenter, single-arm, phase 2 design. The study protocol was approved by the institutional review boards of all participating institutions, and written informed consent to treatment was obtained from all patients before trial entry. This trial was registered with the UMIN clinical trials registry.

Patients

Patients with operable cervical esophageal cancer fulfilling the following criteria were enrolled: histologically confirmed squamous cell carcinoma of cervical esophagus; age 20 to 75 years; Eastern Cooperative Oncology Group performance status between 0 and 1; normal organ function; and N0-1 disease, including superior mediastinum lymph nodes above the tracheal bifurcation.
With regard to location of the primary disease, patients were excluded if the upper aspect of the tumor extended cranially beyond the level of the hyoid or if the lower end extended caudally beyond the aortic arch. Patients with T1 disease who were candidates for endoscopic resection or who were not candidates for laryngectomy were also excluded.

Pretreatment clinical evaluation included air contrast barium esophagography; upper gastrointestinal endoscopy; and cervical, chest, and abdominal computed tomography. Radiologic evaluation for staging was jointly reviewed by radiologists, surgeons, and oncologists. Tumor staging was performed using the 6th edition of the International Union Against Cancer TNM classification. Positron emission tomography (PET) was not used routinely because of domestic reasons (routine use of PET—computed tomography for staging and response evaluation was not accepted by government health insurance).

**Treatment regimens**

The treatment protocol consisted of concurrent CRT and additional chemotherapy (CT) (Fig. 1).

First, patients received concurrent CRT with 5-FU plus CDDP. Our protocol permitted the construction of a percutaneous endoscopic gastrostomy before the start of CRT. Chemotherapy consisted of 5-FU at a dose of 700 mg/m² intravenous on days 1 to 4 and CDDP at 70 mg/m² intravenous on day 1, repeated every 4 weeks for 2 cycles. Radiation therapy consisted of 60 Gy in 30 fractions over 6 weeks, delivered with megavoltage equipment (≥6 MV) using the multiple-field technique. Computed tomography–based 3-dimensional treatment planning was required for all enrolled patients. The initial clinical target volume (CTV1) included the primary tumor with a 2-cm margin for subclinical cranio-caudal extension, metastatic lymph nodes, and regional lymph nodes. The initial planning target volume (PTV1) was defined as the CTV1 plus 1 to 2 cm cranio-caudally and 0.5 to 1 cm circumferentially, with compensation for internal organ motion and daily setup variation. The lower neck, supraclavicular, upper mediastinal, and subcarinal lymph nodes were included in the prophylactic irradiation field. The boost CTV (CTV2) included the primary tumor with a 1- to 2-cm margin for subclinical cranio-caudal extension and metastatic lymph nodes. The boost PTV (PTV2) included CTV2 with adequate margins. The PTV1 was irradiated with up to 40 Gy in 20 fractions, before a booster dose of 20 Gy in 10 fractions was delivered to PTV2. Irradiation using 4 or more portals was strongly recommended to avoid excessive dosing to the spinal cord near the primary site. Dose constraints for normal tissue were defined as follows: spinal cord, <48 Gy; and lung, V₁₀ <50%, V₁₅ <40%, and V₂₀ <25% (CRT phase).

For patients achieving an objective response after CRT, 2 additional cycles of CT with 5-FU (800 mg/m², days 1-5) and CDDP (80 mg/m², day 1) were repeated at 4-week intervals, starting 4 weeks after the completion of CRT (CT phase). When a patient achieved complete response (CR) after the completion of additional CT, additional treatment was not permitted unless recurrence was observed. When a patient had persistent disease or recurrence after completion of CRT, 2 additional cycles of CT with 5-FU (800 mg/m², days 1-5) and CDDP (80 mg/m², day 1) were repeated at 4-week intervals, starting 4 weeks after the completion of CRT (CT phase). When a patient achieved complete response (CR) after the completion of additional CT, additional treatment was not permitted unless recurrence was observed. When a patient had persistent disease or recurrence after completion

![Fig. 1. Protocol treatment schema. The treatment protocol consisted of concurrent chemoradiotherapy (CRT) and additional chemotherapy (CT). Additional CT was limited to patients who achieved an objective response after CRT. Abbreviations: 5-FU = 5-fluorouracil; CDDP = cisplatin; RT = radiation therapy.](image-url)
of additional CT, salvage surgery was considered as post-protocol treatment.

The CRT phase was defined from the initiation of radiation therapy to 2 weeks after the end of radiation therapy. The CT phase was defined from day 1 of additional 5-FU/CDDP to 8 weeks after day 1 of additional 5-FU/CDDP.

**Assessment of response evaluation**

For lymph node metastases and new lesions, response was evaluated according to Response Evaluation Criteria in Solid Tumors version 1.0 with CT. Positron emission tomography was not used.

Response evaluation of the primary site was done using endoscopic evaluation criteria (20) when observation of the entire esophagus satisfied all of the following criteria: (1) disappearance of the tumor lesion; (2) disappearance of ulceration (slough); and (3) absence of cancer cells in biopsy specimens. An evaluation of CR was not obviated by the presence of erosion, a granular protruded lesion, ulcer scar, or Lugol-voiding lesion.

The first evaluation was carried out 28 days after the completion of CRT, and the second after the completion of 4 cycles of CT (21). Endoscopic assessments were repeated every 4 weeks until primary CR or progressive disease was confirmed.

**Assessment of toxicities**

Toxicities were graded using the Common Terminology Criteria for Adverse Events version 3.0.

In the present study, toxicity profiles in the CRT and CT phases were reported separately. Basically, late toxicity was reported in periodic monitoring every 12 months using the case report form.

**Follow-up**

After CR in the primary site and lymph nodes was confirmed, radiologic and endoscopic evaluations were performed in accordance with the follow-up program prescribed in the protocol (File E01; available online at www.redjournal.org).

**Endpoints and statistical analyses**

The primary endpoint of this study was 3-year overall survival rate. Because prospective data were scarce, we estimated 3-year overall survival rate from a retrospective study (19) as 40%. When 3-year overall survival rate was below 20%, the study treatment was to considered to provide insufficient organ preservation as an alternative to surgery. Accordingly, the expected 3-year overall survival rate and threshold were set at 40% and 20%. With 80% power and a 1-sided type 1 error of 5%, the minimum number of patients required to evaluate the primary endpoint was 32. Allowing that 10% of patients might be excluded by protocol violation or other reasons, we calculated a total sample size of 35 patients.

Overall survival time was calculated from the start of treatment to the date of death or the last confirmed date of survival. Survival time was censored at the last confirmed date of survival if the patient was alive. Progression-free survival (PFS) time was defined from the day of initiation of treatment to the first day of confirmation of progressive disease at any site or any cause of death. Laryngectomy-free survival (LFS) time was calculated from the start of treatment to the first day of confirmation of laryngectomy or any cause of death. Overall survival time, PFS time, and LFS time were estimated by the Kaplan-Meier product-limit method using commercially available statistical software (StatView version 5.0, SAS Institute, Cary, NC).

The correlation of T stage with overall survival, PFS, and LFS was investigated using the log-rank test.

**Results**

**Patients**

Recruitment was discontinued early because of slow accrual. From January 2009 through August 2012, 33 patients were enrolled across 8 sites in Japan. Three patients were excluded from analysis because of patient discretion (n = 1) and a change in strategy before the start of protocol treatment (n = 2). The remaining 30 patients are characterized in Table 1. Eighteen patients had stage III to IV disease, and of those, 13 had T4 disease.

**Safety profile**

Twenty-nine of 30 patients (97%) completed radiation therapy. Median duration of radiation therapy was 43.5 days.

### Table 1 Patient characteristics (n = 30)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age (y), median (range)</td>
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<td>Sex (n), male/female</td>
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<td>Performance status (n), 0-1/2</td>
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<tr>
<td>IV (n = 5)</td>
<td>T3N1M0, n = 3</td>
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</tbody>
</table>

* Upper mediastinal lymph node metastases.
Twenty-eight patients received a full dose of CT during radiation therapy. Relative dose intensity in the CRT phase was 98.1% for CDDP and 99.4% for 5-FU. One patient developed a grade 4 fistula of the esophagus during radiation therapy and stopped protocol treatment.

The average pre- and post-CRT weight of all patients was 58.6 kg (range, 37.4-81.4 kg) and 54.5 kg (range, 35.8-77.2 kg), respectively.

Median percentage of weight loss during CRT was 6.4% (range, 0.2%-13.4%). Grade 2 weight loss (>10% weight loss) occurred in 7 patients, whereas no grade 3 weight loss (>20%) was seen.

Twenty-three patients received at least 1 course of additional CT. Drop-out was due to duodenal ulcer in 1, worsened performance status in 2, progressive disease in 2, hearing loss in 1, and patient refusal in 2. Nineteen patients received 2 courses of additional CT, and relative dose intensity in the CT phase was 56.0% for CDDP and 57.1% for 5-FU. Seven cases (7 of 23, 30.4%) developed grade 3 neutropenia, whereas there was no case of febrile neutropenia. One grade 4 thrombocytopenia was seen in the CT phase.

Toxicity profile in the CRT and CT phases is outlined in Table 2. No treatment-related death was seen in either the CRT or CT phase.

### Efficacy

The overall CR rate was 73.3% (22 of 30), and the CR rate at the primary site was 76.7% (23 of 30). With a median follow-up period of 40.8 months, 3-year overall survival was 66.5% (95% confidence interval 40.6%-77.3%). Three-year PFS and LFS rates were 36.6% and 52.5%, respectively (Fig. 2).

Three-year overall survival in patients with overall CR was 74.6%, whereas that in patients with overall non-CR was 25.0%, with this difference being significant ($P = .002$) (Fig. 3).

### Failure pattern and second-line treatment

Eleven patients showed no recurrence on follow-up. In those with recurrence, the initial failure pattern was local recurrence only in 9, local recurrence with lymph node metastases in 2, local recurrence with distant metastases in 2, lymph node metastases only in 4, and distant metastases in 2. With regard to the 13 patients with local recurrence, 5 patients underwent salvage surgery, and 3 remained alive for more than 3 years. One patient received photodynamic therapy and was alive with an intact larynx. Three patients received CT, and the remaining 3 received no further anticancer treatment. Outcomes are listed in File E02 (available online at www.redjournal.org).

There were a total of 15 events of local failure in the present study, and there were 7 events of distant failure and 7 patients who died without distant failure.

The 3-year local failure-free survival rate estimated by the Kaplan-Meier product-limit method was 43.3% (Fig. 3).

### Late toxicity and cause of death

With regard to late toxicity, 5 cases of grade 1 radiation pneumonitis have been reported at this point, and no fatal pneumonitis has been seen. Four patients without disease have received endoscopic dilatation of the esophagus because of esophageal stenosis after CRT.

Twelve patients died during study observation, 11 due to progressive disease and 1 due to another cause (pancreatic cancer).
Correlation of T stage and survival

Among the 13 patients with T4 disease, CR rate at the primary site was 53.8% (7 of 13). Four of 6 patients with residual disease at the primary site received salvage surgery, of whom 2 survived.

Regarding laryngeal preservation, laryngectomy-free survival tended to be worse with T4 disease, albeit without statistical significance ($P = .10$), whereas no significant difference was seen in 3-year overall survival ($P = .34$).

Discussion

This is the first prospective study of CRT for cervical esophageal cancer. With active median follow-up of 40.8 months, 3-year overall survival and LFS were 66.5% and 52.5%, respectively. The overall CR rate was 73.3% (22 of 30), and 3-year overall survival in patients with overall CR was 74.6%.

For T4 disease, the overall CR rate was 54% and 3-year overall survival and LFS were 58.3% and 38.5%, respectively.

Accordingly, CRT has sufficient efficacy and safety to be considered an alternative treatment to surgery in patients with cervical esophageal cancer.

Because the cervical esophagus is located closely anterior to the spinal cord, providing sufficient radiation dosage for the posterior wall of the esophagus while sparing the spinal cord using the conventional technique is difficult. It is therefore necessary to take advantage of qualified radiation techniques, such as conformal radiation therapy. Although we used a 3-dimensional multiple-field technique in the present study, intensity modulated radiation therapy may also solve the problem of proximity and be easier in current clinical practice.

Fig. 2. Survival. Kaplan-Meier plots of overall, progression-free, and laryngectomy-free survival. Minimum follow-up period in patients alive at data fixation was 759 days.
Relative dose intensity in the CRT phase was 98.1% for CDDP and 99.4% for 5-FU, and was thus considered sufficient. We initially considered that acute toxicities (mucositis and dermatitis) might be more frequent with cervical esophageal cancer and had set the CDDP and 5-FU dosages slightly below the 75 to 100 mg/m² for CDDP on day 1 and 750 to 1000 mg/m² for 5-FU on days 1 to 4 recommended for thoracic esophageal cancer. Further improvement in the dose setting of these anticancer agents seems possible.

Median percentage of body weight loss during CRT was 6.4% (range, 0.2%-13.4%), and >10% weight loss occurred in 7 patients (23.3%). In our protocol, although construction of a percutaneous endoscopic gastrostomy before the start of CRT was permitted, nutritional management was not described in detail. If nutritional management had been considered in detail, the frequency of grade ≥2 weight loss might have been reduced. The lack of nutritional information in detail is one of the limitations in this study.

Although a phase 3 study would always be preferable, the infrequency/rarity of cervical esophageal cancer may render this all but impossible. At the planning stage, we expected our study would be considered among the highest-level evidence available for this condition, and even though it was a phase 2 study, we selected overall survival as an optimal index for primary endpoint.

Among the few articles on surgical approaches involving more than 50 patients reported to date, Triboulet et al (14) reported a 3-year overall survival rate in 78 cases of cervical esophageal cancer of 22%, whereas a recent study
from Japan reported a 3-year overall survival rate in 74 cases of 42%. Several groups reported a significantly worse prognosis for cervical esophageal cancer than hypopharyngeal cancer using a surgical approach (13, 14, 17). Our present results are substantially better than these historical controls, even allowing for differences in background factors.

Laryngeal preservation is an important aim for patients with carcinoma of the hypopharynx, larynx, and cervical esophagus. In the present study the 3-year LFS rate was 52.5% for all T stages, and 38.5% for T4 disease. Our protocol treatment can play an important role in laryngeal preservation in patients at any T stage.

In contrast, 9 patients underwent salvage surgery after CRT.

No severe complication occurred in salvage surgery, and 6 patients (66%) remain alive at writing without disease after salvage surgery. Our results showed that even if the laryngeal preservation strategy fails, some patients can achieve a disease-free status by salvage surgery. Chemoradiotherapy as an initial treatment can achieve a sufficiently good outcome only after appropriate salvage treatment support.

Two recent large-scale retrospective studies of nonsurgical approaches for cervical esophageal cancer (11, 12) provide substantial information to guide clinical practice, but differed with regard to failure sites. Cao et al (12) reported that the main site of failure was the primary site in 115 cervical esophageal cancer patients treated with (chemo)radiotherapy. In contrast, Zhang et al (11) reported that the main site was not the primary site but a distant organ in 102 cervical esophageal cancer patients treated with platinum-based CRT. We speculate that one cause of these contradictory results may be that these retrospective studies inadvertently included patients with hypopharyngeal cancer, in whom the field setting for prophylactic lymph node irradiation might have been insufficient. In any case, the main initial site of failure in our study was the primary site, and distant metastasis as a first failure site was seen in only 4 patients (4 of 30, 13.3%).

Three major limitations of our study warrant mention. First is the proportion of cases of different tumor stages. Because this is a rare disease, we could not expect to enroll an optimum range of patients before the start of the study. To minimize the biases arising from this limitation, our protocol required that patients with T1 disease who were candidates for endoscopic resection or who were not candidates for laryngectomy should also be excluded. In our study, 11 early-stage (I/II) patients were included, but all were candidates for total laryngectomy who requested laryngeal preservation. Previous retrospective studies have also included early-stage patients in their reported clinical outcomes. A historical comparison of patient characteristics and outcomes from previous reports is shown in Table 3.

Second, recruitment had to be discontinued early owing to slow accrual. The main reason is the very low occurrence of cervical esophageal cancer. Similarly, Triboulet et al’s study (14) required 17 years to recruit 78 patients (4.6 cases per year). Complete accumulation would likely have taken an additional year; and given the good results obtained, this lower number did not impact the statistical analysis. We therefore decided to close the study early and publish the data available at that time.

Third was the difference of tumor staging and response evaluations. Tumor staging was performed using the 6th edition of International Union Against Cancer TNM classification because this study was conducted from 2007. Additionally, PET–computed tomography for staging or response evaluation was not used routinely, because in Japan, not all institutions provided this examination routinely in 2007, and routine use of PET–computed tomography for staging and response evaluation was not accepted by government health insurance.

These may be slightly different from current clinical practice in United States and other countries.

In conclusion, our study, the first prospective trial of CRT for cervical esophageal cancer, showed that CRT has sufficient efficacy and safety to be considered an alternative to surgery in these patients. Development of CT regimens or radiation techniques may improve clinical outcomes in the near future. Given this condition’s status as an orphan disease, further multicenter and multination prospective investigations are mandatory.

Table 3 Published previous reports about outcomes of cervical esophageal cancer

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study design</th>
<th>N</th>
<th>Stage I/II/III/IV</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Burmeister</td>
<td>2000</td>
<td>Retrospective</td>
<td>34</td>
<td>4/20/7/3</td>
<td>5-FU/CDDP/RT</td>
<td>5YOS 55%</td>
<td>3 different CRT regimens</td>
</tr>
<tr>
<td>Cao</td>
<td>2014</td>
<td>Retrospective</td>
<td>161</td>
<td>1/46/114/0</td>
<td>RT or CRT</td>
<td>2YOS 47.6%</td>
<td>Median follow-up period: 17.1 mo</td>
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<tr>
<td>Zhang</td>
<td>2015</td>
<td>Retrospective</td>
<td>102</td>
<td>0/32/70/0</td>
<td>Platinum-based CRT</td>
<td>3YOS 39.3%</td>
<td>Main failure site: primary site</td>
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<tr>
<td>Triboulet</td>
<td>2001</td>
<td>Retrospective</td>
<td>78</td>
<td>-</td>
<td>Surgery + (RT)</td>
<td>3YOS 22%</td>
<td>Hypopharyngeal extention: 22.5%</td>
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<tr>
<td>Daiko</td>
<td>2007</td>
<td>Retrospective</td>
<td>74</td>
<td>6/30/38/0</td>
<td>Surgery</td>
<td>3YOS 42%</td>
<td>Main failure site: DM</td>
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<td>Present study</td>
<td>2016</td>
<td>Phase 2</td>
<td>30</td>
<td>2/9/13/15</td>
<td>5-FU/CDDP/RT</td>
<td>3YOS 66.5%</td>
<td>20 patients had T1 disease</td>
</tr>
</tbody>
</table>

Abbreviations: 3YOS = 3-year overall survival; 5-FU = 5-fluorouracil; 5YOS = 5-year overall survival; CDDP = cisplatin; CRT = chemoradiotherapy; DM = distant metastases; RT = radiation therapy; TE = total esophagectomy; TP = total pharyngectomy.
References