Original Investigation

Primary Radiotherapy Compared With Primary Surgery in Cervical Esophageal Cancer

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IMPORTANCE The management of cervical esophageal cancer (CEC) is controversial. The advantages of radiotherapy (RT) for CEC are lower rates of acute morbidity and mortality compared with surgery and potential for larynx preservation. The advantage of surgery is that the transposed stomach may function better over the long term than an irradiated esophagus, which tends to become stenotic over time. Which one is the primary treatment of CEC?

OBJECTIVE To evaluate treatment outcomes of primary RT and primary surgery in patients with CEC.

DESIGN, SETTING, AND PARTICIPANTS This retrospective study conducted in a university hospital included 224 patients treated for CEC between 2001 and 2012.

INTERVENTIONS One hundred and sixty-one patients who received primary RT with or without subsequent surgery were assigned to the RT group, including 133 patients who received RT alone or RT with concurrent chemotherapy and 28 patients who received preoperative RT plus surgery. Sixty-three patients who received primary surgery with or without subsequent RT were assigned to the primary surgery group, including 27 patients who received surgery alone and 36 patients who received surgery plus postoperative RT.

MAIN OUTCOMES AND MEASURES The rates of overall 2-year local failure-free survival (FFS), regional FFS, distant FFS, and overall survival for patients undergoing primary RT and primary surgery were compared. A separate analysis using matched cases between the primary RT group and primary surgery group was conducted.

RESULTS The median follow-up time was 15.1 months. The rates of overall 2-year local FFS, regional FFS, distant FFS, and overall survival for patients undergoing primary RT and primary surgery were 69.9% and 68.6%, 79.5% and 69.8%, 74.3% and 62.5%, 49.3% and 50.7%, respectively (P > .05 for all). Matched-case analyses did not show any significant differences in measured survival rates between the treatment groups.

CONCLUSIONS AND RELEVANCE Given the similarities in rates of local FFS, regional FFS, distant FFS, and overall survival between the primary RT and primary surgery CEC treatment groups, we recommend primary RT for larynx preservation, with surgery offered subsequently for patients who do not respond to RT.

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Cervical esophageal cancer (CEC) is relatively uncommon, representing less than 5% of all esophageal cancer. Not surprisingly, limited information is available on the outcomes of CEC treatment.

The management of CEC is controversial. The choice of treatment has been surgical resection, radiation therapy (RT), or a combination of the two. The advantages of RT are lower rates of acute morbidity and mortality compared with surgery and potential for larynx preservation. The advantage of surgery is that the transposed stomach may function better over the long term than an irradiated esophagus, which tends to become stenotic over time. Ideally, answers to this question would be obtained through prospective, multiinstitutional studies. In the absence of such class I evidence, therapeutic decisions must be made on the basis of retrospective studies. The aim of this study is to evaluate treatment outcomes of primary RT and primary surgery in patients with CEC.

### Methods

#### Patients and Patient Workup

The independent ethics committee of the Cancer Hospital of the Chinese Academy of Medical Sciences, Peking Union Medical College, approved the case recording system used to identify medical records of patients diagnosed with CEC in our center from January 2001 through April 2012. Owing to the retrospective nature of the study, patient informed consent was waived.

During the years 2001 through 2012, 244 patients were diagnosed with CEC. Of these 244 patients, 20 were excluded from the present analysis for incomplete pretreatment workup (n = 5), nonregional nodal metastases (n = 9), and systemic metastases at presentation (n = 6). Our retrospective analysis included the remaining 224 patients.

### Table 1. Clinical Characteristics of All and Matched Cases

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<tr>
<th>Characteristic</th>
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<th>Case-Matched Patients (n = 116)</th>
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<td>Metachronous</td>
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<td>8</td>
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</table>

Abbreviations: CE, cervical esophagus; HP, hypopharyngeal extension; PRT, primary radiotherapy alone or with chemotherapy; PS, primary surgery; SCC, squamous cell carcinoma; TE, thoracic esophageal extension.

*a Grading of dysphagia was as follows: 0, none; 1, mild dysphagia but can eat regular diet; 2, dysphagia requiring predominantly pureed, soft, or liquid diet; 3, dysphagia requiring intravenous hydration.*
The pretreatment workup included a complete history and physical examination, liver and renal biochemical analysis, complete blood cell count, barium contrast study, endoscopy, computed tomography (CT) scans of the neck and thorax, and ultrasonography of the abdominal and cervical regions with or without fine-needle aspiration cytology when cervical nodal metastasis was detected. Endoscopic ultrasonography and positron emission tomography fusion with CT scans were used beginning September 2007. In addition, bronchoscopy was performed for patients with locally advanced diseases unless the patient’s condition was not suitable or the patient declined. All patients underwent disease staging using the 2002 American Joint Committee on Cancer staging system. Patients in the primary RT group, treated with RT alone, RT with concurrent chemotherapy, or preoperative RT plus surgery, were compared with those in the primary surgery group, who were treated with surgery alone or surgery plus postoperative RT. The clinical characteristics of all patients are listed in Table 1.

**Treatment Protocol**

In our center, preoperative RT was performed in patients with locally advanced CEC. Definitive RT was performed in patients with adequate response to preoperative RT. Although definitive chemoradiotherapy with fluorouracil and cisplatin was the standard of care for patients with esophageal cancer, study protocol was not recorded for the use of concurrent chemotherapy, which was used at discretion of the attending physician in individual cases. Surgery was to be performed on patients who did not respond after completion of RT (preferably within 3 to 5 weeks). Early-stage CEC may be treated with primary surgery, and selective postoperative RT was to be performed according to the pathologic assessment.

In this study, 133 patients received RT alone or RT with concurrent chemotherapy; 28 patients received preoperative RT plus surgery; 27 patients received surgery alone; and 36 patients received surgery plus postoperative RT. Fifty-one patients received concurrent cetuximab or nimotuzumab, and 1 patient in the primary RT group was given concurrent Tarceva (Genentech). After definitive RT with concurrent chemotherapy, 1 patient underwent salvage pharyngo-laryngo-esophagectomy (PLE) for palliation of grade 3 dysphagia, and 11 patients underwent salvage PLE for local failure.
Treatment in the Primary RT Group
Among the 161 patients in the primary RT group, 61 were irradiated using conventional techniques by anteroposterior opposing fields or oblique fields at a daily dose of 2 Gy; 18 were irradiated using 3-dimensional conformal RT at a daily dose of 1.8 to 2.0 Gy; and 82 patients were treated using intensity-modulated RT at a daily dose of 2.00 to 2.12 Gy to the gross tumor volume. The field of irradiation covered the gross tumor with an additional radial margin of at least 1 cm and longitudinal margin of at least 3 cm. Adjacent involved lymph nodes, if any, were included in the radiation field.

Of the patients treated with RT alone, 80 received a median dose of 68 Gy (range, 60-80 Gy); 10 received a total dose of only 6 to 56 Gy (at the discretion of the attending physician or because the patient refused further RT); 2 with esophageal perforation received a total dose of 52 to 54 Gy; and 2 with pneumonia received a total dose of 54 to 58 Gy. Of the patients treated with RT and concurrent chemotherapy, 35 received a median dose of 64.0 Gy (range, 59.4-76.0 Gy); 3 with upper gastrointestinal hemorrhage, acute laryngopharynx, or esophageal perforation received a total dose of 28.8 to 50.4 Gy; and 1 patient who elected to terminate RT received a total dose of 50 Gy. Twenty-eight patients who were treated with preoperative RT received a total dose of 40 to 50 Gy.

Patients with no response to preoperative RT underwent surgery unless the patient’s condition was not suitable or if the patient declined. Patients with response to preoperative RT were continued RT unless they chose not to. A clinical complete response was defined as the absence of dysphagia and of visible tumor on barium contrast study; a partial response was defined as a decrease of more than 30% of the tumor length on esophagogram, which is the World Health Organization definition of partial response for unidimensionally measurable lesions and improvement of dysphagia.

Treatment in the Primary Surgery Group
Among the 63 patients treated with primary surgery, 27 received surgery alone, while 36 received surgery plus postoperative RT. Patients treated with postoperative RT received a median dose of 50 Gy (range, 45-60 Gy). Fifty-two patients underwent PLE, and 11 underwent surgery with larynx preservation. The PLE was performed by first mobilizing the esophagus using a transthiatal or thoracoscopic approach. The larynx, pharynx, and cervical esophagus were resected. Open lapa-
Rototomy was used for the abdominal phase of the operation. The stomach or the free jejunal transplant was the conduit of choice to restore gastrointestinal continuity. Selective neck dissection was performed for all the patients. Patients with 2 or more involved nodes, positive margins, extracapsular nodal spread of tumor, stage T3 to T4 or histologic grade 3 disease were given postoperative RT unless the patient’s condition was not suitable or the patient declined.

Treatment Monitoring
All patients were evaluated weekly during RT and followed up after the completion of treatment according to the following schedule: 1 month after the completion of treatment, every 3 months in the first 2 years after treatment, every 6 months from year 3 through year 5, and annually thereafter. Each follow-up included a complete examination including basic serum chemical analysis, barium contrast study, and ultrasonography of the abdominal region and the cervical region. Also, CT scans of the neck and thorax and endoscopy studies were performed upon completion of treatment and every 6 months thereafter. Radiotherapy-induced toxic effects were assessed and scored at each follow-up according to the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria.12

Statistical Analyses
The Statistical Package for Social Sciences, version 17.0 (SPSS IBM Corp), was used for statistical analysis. The rates of local failure-free survival (FFS), distant FFS, regional FFS, and overall survival were estimated by use of the Kaplan-Meier method. Rates of local, distant, and regional FFS and overall survival were measured from day 1 of treatment to the date of the event. The log-rank test was used in univariate analysis to assess differences between the primary RT and the primary surgery groups, and the Cox regression method was used in multivariate analysis. The χ², Fisher exact, and t tests were used to compare the differences between the 2 treatment groups. Statistical tests were based on a 2-sided significance level. P < .05 indicated statistical significance.

Because there were more patients with stage III disease in the primary RT group than in the primary surgery group (P = .02), we used SAS software, version 9.2 (SAS Institute LP), to conduct a matched-case analysis. For this analysis, patients were matched between treatment groups for age (within 5 years), sex, histologic grade, and stage to reduce the effects of patient selection bias on the end points measured in this study.

Results

Treatment Outcomes
The median follow-up time in surviving patients was 22.1 months (range, 0.4-130.9 months). For all patients, the rates of overall 2-year local, regional, and distant FFS and overall survival were 69.7%, 77.0%, 71.4%, and 49.7%, respectively. The overall 2-year local FFS rates for patients in the primary RT and primary surgery groups were 69.9% and 68.6%, respectively (P = .86). The overall 2-year regional FFS rates for patients in the primary RT and primary surgery groups were 79.5% and 69.8%, respectively (P = .15). The overall 2-year distant FFS rates for patients in the primary RT and primary surgery groups were 74.3% and 62.5%, respectively (P = .66). The overall survival rates for patients in the primary RT and primary surgery groups were 49.3% and 50.7%, respectively (P = .31) (Figure 1).

Table 2. Complications Occurring in Patients Who Underwent Surgery for Cervical Esophageal Cancer

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<thead>
<tr>
<th>Complication</th>
<th>Patients, No. (n = 103)</th>
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<tr>
<td>Arrhythmia</td>
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<td>Heart failure</td>
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<tr>
<td>Respiratory failure</td>
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<tr>
<td>Acute renal failure</td>
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</tr>
<tr>
<td>Septic shock</td>
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</tr>
<tr>
<td>Hypovolemic shock</td>
<td>1</td>
</tr>
<tr>
<td>Disseminate intravascular coagulation</td>
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</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
</tr>
<tr>
<td>Stress ulcer</td>
<td>3</td>
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<tr>
<td><strong>Surgical</strong></td>
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<tr>
<td>Wound problem</td>
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<tr>
<td>Hemorrhage</td>
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<tr>
<td>Bilateral vocal cord paralysis</td>
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<td>Anastomatic leakage</td>
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<tr>
<td>Gastroplegia</td>
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</tr>
<tr>
<td>Reexploration</td>
<td>8</td>
</tr>
<tr>
<td>Graft failure</td>
<td>2</td>
</tr>
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</table>
Because of the statistically significant differences in the tumor stage between the primary RT group and the primary surgery group, 58 patients in each group were matched for age (within 5 years), sex, histologic grade, and stage to reduce the effect of the selection bias on the outcome. The 2-year overall survival rates in this case-matched comparison were 55.6% and 47.7%, respectively (P = .71), for the primary RT and primary surgery groups. Similarly, no significant differences were observed between the 2 groups in any FFS rate (local, P = .31; regional, P = .13; and distant, P = .41) (Figure 2).

By their last follow-up visit, 100 patients had developed treatment failure. Of these 100 patients, 35, 7, and 22 had developed local failure, regional failure, and distant metastasis, respectively, and 8 had developed distant metastasis and failure at the primary and nodal site. The categories of these 100 patients with treatment failure are illustrated in Figure 3. The metastatic sites included the lung in 26, the bone in 15, the liver in 6, the brain in 1, the subcutis in 3, the pleura in 3, the mediastinal lymph nodes in 12, and other distant lymph nodes in 10 patients.

Treatment Complications
For the patients treated with primary RT: the most frequently observed acute toxic effects were mainly grade 1 or grade 2. The incidences of acute grade 3 mucositis (including pharyngitis), skin reaction, and leukopenia were 4.3%, 7.5%, and 6.2%, respectively. Seven patients required RT terminations (upper gastrointestinal hemorrhage in 1, acute laryngemphraxis in 2, pneumonia in 2, and esophageal perforation in 3).

Grade 3 dysphagia was recorded in 9 (5.6%) of the 161 patients, but in 1 of these, the grade 3 dysphagia preceded treatment. One patient died of carotid blowout syndrome 8 months after treatment. One patient died of upper gastrointestinal hemorrhage 1 month after RT termination for esophageal perforation.

Table 3. Impact of Prognostic Characteristics on Treatment Results by Univariate Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Local FFS*</th>
<th>Regional FFS*</th>
<th>Distant FFS*</th>
<th>Overall Survival*</th>
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<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
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<tr>
<td>Sex</td>
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Abbreviations: FFS, failure-free survival; PRT, primary radiotherapy alone or with concurrent chemotherapy; PS, primary surgery.

*All survival measurements are for 2 years.

b For an explanation of dysphagia grades, see footnotes of Table 1.
tion. Four (2.5%) had hypothyroidism requiring lifelong thyroxine replacement.

The medical and surgical complications after surgery are listed in Table 2. The 30-day mortality rate was 4.9% (n = 5). Among these 5 patients, 2 had been treated with RT alone, receiving a total dose of 70 Gy, and had developed local failure; 2 received preoperative RT; and 1 patient received primary surgery.

For the patients treated with primary surgery, 5 (7.9%) had developed grade 3 dysphagia for anastomotic stenosis; 1 had gastrotrhagia after postoperative RT; and 2 patients, including 1 who received surgery alone, had hypothyroidism requiring lifelong thyroxine replacement.

Prognostic Factors
The value of various potential prognostic factors including age, sex, hoarseness, dysphagia, weight loss, hypopharyngeal extension, thoracic esophageal extension, histologic grade, stage, and primary treatment on predicting local, regional, and distant FFS and overall survival were evaluated. The outcomes are reported in Table 3 and Table 4.

Discussion
To our knowledge, the present study is the first to evaluate treatment outcomes of primary RT and primary surgery in patients with CEC. The reported outcomes of CEC treated with primary surgery at different centers are listed in Table 5.2-5 The 5-year survival rates found in these investigations ranged from 14% to 31.2%, which is similar to the results found in our primary surgery group. Reported operative mortality rates range from 1.6% to 13.5%. For patients treated with primary RT, the reported 5-year locoregional CEC control rates of range from 25.8% to 47.7% and the 5-year overall survival rates from 17% to 55%. The outcomes for primary RT treatment of CEC from different medical centers are listed in Table 6.5-10

Table 4. Impact of Prognostic Characteristics on Treatment Results by Multivariate Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Local FFS*</th>
<th>Regional FFS*</th>
<th>Distant FFS*</th>
<th>Overall Survival*</th>
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<td>.91</td>
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<td>Weight loss, %</td>
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<td>.98</td>
<td>.90</td>
<td>.04</td>
</tr>
<tr>
<td>Hypopharyngeal extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs yes</td>
<td>.86</td>
<td>.65</td>
<td>.16</td>
<td>.06</td>
</tr>
<tr>
<td>Thoracic esophageal extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs yes</td>
<td>.74</td>
<td>.44</td>
<td>.94</td>
<td>.88</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 vs 1,2,x</td>
<td>.93</td>
<td>.41</td>
<td>.69</td>
<td>.75</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II vs III-IV</td>
<td>.18</td>
<td>.39</td>
<td>.16</td>
<td>.001</td>
</tr>
<tr>
<td>Primary treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRT vs PS</td>
<td>.96</td>
<td>.24</td>
<td>.31</td>
<td>.67</td>
</tr>
</tbody>
</table>

Abbreviations: FFS, failure-free survival; PRT, primary radiotherapy alone or with concurrent chemotherapy; PS, primary surgery.
* All survival measurements are for 2 years.

Table 5. Results of Primary Surgery for Cervical Esophageal Cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Operative Mortality</th>
<th>2-Year Overall Survival</th>
<th>5-Year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kakegawa et al,4 1985</td>
<td>64</td>
<td>11.0</td>
<td>NA</td>
<td>27.0</td>
</tr>
<tr>
<td>Triboulet et al,2 2001</td>
<td>78 (131)</td>
<td>4.8a</td>
<td>NA</td>
<td>14.0</td>
</tr>
<tr>
<td>Nishimaki et al,3 2002</td>
<td>32 (20)x</td>
<td>13.5a</td>
<td>NA</td>
<td>31.2b</td>
</tr>
<tr>
<td>Tong et al,5 2011</td>
<td>62</td>
<td>1.6</td>
<td>37.6</td>
<td>NA</td>
</tr>
<tr>
<td>Present study</td>
<td>68</td>
<td>1.5</td>
<td>50.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CEC, cervical esophageal cancer; NA, not available; OS, overall survival.
* Data are reported as number of CEC cases (number of hypopharyngeal cancer cases).
† Reported results from combined CEC and hypopharyngeal cancer cases.
therapy followed by surgery with the same induction chemotherapy followed by chemoradiotherapy without surgery, no significant difference was found in overall survival between the 2 treatment groups. Local progression-free survival was better in the surgery group (2-year progression-free survival, 64.3%) than in the chemoradiotherapy group (2-year progression-free survival, 40.7%). Treatment-related mortality was significantly greater in the surgery group than in the chemoradiotherapy group (12.8% vs 3.5%; P = .03). Also, a meta-analysis investigating RT vs surgery within multimodality protocols for esophageal cancer indicated that overall survival was equivalent between surgery and definitive chemoradiotherapy. In our study, patients with no response to preoperative RT underwent surgery, and no significant differences were found in overall survival or local, distant, or regional FFS between the primary RT group and the primary surgery group.

With respect to organ preservation, treatment approaches such as chemotherapy, RT, concurrent chemotherapy and RT, and targeted therapy have been used to preserve the functional larynx for patients with laryngeal or hypopharyngeal cancer. Recent advances in radiation oncology and treatment planning have led to the implementation of intensity-modulated RT. Wang et al describe 6 patients who achieved complete remission after treatment with intensity-modulated RT and concurrent chemotherapy for locally advanced cervical and upper thoracic esophageal cancer.

Direct comparison between the 2 treatment modalities is difficult. Selection bias is obviously evident in studies of this kind, and a randomized clinical trial is unlikely to be feasible. Comparative study of overall quality of life using validated instruments during and after treatment is lacking. When faced with the potential for larynx preservation, most patients would probably opt for RT.

Conclusions

The current study finds no significant difference in rates of local, regional, or distant FFS or overall survival between the primary RT group and the primary surgery group, and both treatments are effective. However, with respect to the potential for larynx preservation, primary RT is recommended, with subsequent surgery offered for patients with no response to preoperative RT.

Table 6. Results of Primary Radiotherapy for Cervical Esophageal Cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Radiation dose, Gy</th>
<th>Con-CT, %</th>
<th>LRC, %</th>
<th>Overall Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendenhall et al, 1988</td>
<td>34</td>
<td>47-75 (mean, 67.5)</td>
<td>No</td>
<td>25.8 (5 y)</td>
<td>34</td>
</tr>
<tr>
<td>Stuschke et al, 1999</td>
<td>17</td>
<td>60-66</td>
<td>Yes</td>
<td>33 (2 y)</td>
<td>24</td>
</tr>
<tr>
<td>Burmeister et al, 2000</td>
<td>34</td>
<td>50.4-65 (mean, 61.2)</td>
<td>Yes, 100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yamada et al, 2005</td>
<td>27</td>
<td>44-73.7 (mean, 66)</td>
<td>Yes, 85.2</td>
<td>13 (5 y)</td>
<td>38</td>
</tr>
<tr>
<td>Wang et al, 2006</td>
<td>22 (13)</td>
<td>24.5-64.8 (median, 50.4)</td>
<td>Yes</td>
<td>47.7 (5 y)</td>
<td>NA</td>
</tr>
<tr>
<td>Tong et al, 2011</td>
<td>21</td>
<td>60-68</td>
<td>Yes, 100</td>
<td>NA</td>
<td>46.9 NA</td>
</tr>
<tr>
<td>Present study</td>
<td>171</td>
<td>59.4-80</td>
<td>Yes, 23.4</td>
<td>69.9 (2y)</td>
<td>51</td>
</tr>
</tbody>
</table>

Abbreviations: Con-CT, concurrent chemotherapy; LRC, locoregional control; NA, not available.

* Disease-free survival.

With upper thoracic esophageal cancer (upper thoracic esophageal cases).


