Esophagectomy for locally advanced esophageal cancer, followed by chemoradiotherapy and adjuvant chemotherapy

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Received: 2004-12-29 Accepted: 2005-02-28

Abstract

AIM: To compare the efficacy and toxicity of a three-step combination therapy with post-operative radiation alone for locally advanced esophageal cancer.

METHODS: Patients with T3-4 and N0-1 esophageal carcinoma from a number of institutions were non-randomly, prospectively enrolled in the study. All patients underwent single-stage curative en bloc esophagectomy. The patients were then assigned into one of two treatment groups based on treatment consisting of either post-operative concurrent chemoradiotherapy (CCRT) with weekly cisplatin 30 mg/m² followed by systemic adjuvant chemotherapy (four monthly cycles of cisplatin 20 mg/m² and 5-fluorouracil 1 000 mg/m² for five consecutive days), or, post-operative radiation alone. The radiotherapy dose was 55-60 Gy for all patients. Primary end-point of this study was to assess the per-protocol patients’ improvement of overall survival benefit. Secondary end-point was designed to evaluate both the per-protocol and intent-to-treat patients’ outcome of survival.

RESULTS: A total of 60 patients (n = 30 per group) were enrolled in this study. The two groups were generally comparable for demographic characteristics and hematological and non-hematological toxicities. The CCRT with weekly cisplatin was well tolerated, with significantly better overall survival (30.9 mo vs 20.7 mo; 95% CI, 27.5-36.4 vs 15.2-26.1) and 3-year survival (70.0% vs 33.7%; P = 0.003). Low histological grade of tumor (P<0.001) was associated with favorable survival in these locally advanced patients.

CONCLUSION: For locally advanced esophageal cancer, the combination of esophagectomy, post-operative CCRT with weekly cisplatin and systemic adjuvant chemotherapy is well tolerated and effective. A large-scale, prospective randomized trial of this regimen is in progress.

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Key words: Curative esophagectomy; Concurrent chemoradiotherapy; Cisplatin

Liu HC, Hung SK, Huang CJ, Chen CC, Chen MJ, Chang CC, Tai CJ, Tzen CV, Lu LH, Chen YJ. Esophagectomy for locally advanced esophageal cancer followed by chemoradiotherapy and adjuvant chemotherapy. World J Gastroenterol 2005; 11(34): 5367-5372
http://www.wjgnet.com/1007-9327/11/5367.asp

INTRODUCTION

Carcinoma of the esophagus often presents at a locally advanced stage. Even with aggressive surgical resection, however, the reported long-term survival rates remain sub-optimal[1]. From analysis of surgical specimens, it appears that a significant proportion of this disease involves regional lymph nodes[2]. In one inter-group comparison report, the local recurrence rate for complete resection was 51%, and the overall local failure rate was 61%[3]. Besides local recurrence, distant metastases of esophageal cancer are another common type of treatment failure.

Several studies have demonstrated that, compared with single modality treatment, a combination of chemotherapy and/or radiotherapy with surgery can improve local control and reduce distant metastases[4-9]. Although post-operative concurrent chemoradiotherapy (CCRT) is reportedly beneficial in terms of outcome in locally advanced diseases such as cervical[10], nasopharyngeal[11], gastric[12], and colorectal[13,14] cancer, by 1998, the role of this type of treatment in post-operative esophageal cancer remains controversia.

An important concern in multi-modal therapy is the greater prevalence of treatment-related complications. Previous CCRT trials for esophageal cancer were hospital-based and used moderate-high doses of cisplatin and 5-fluorouracil (5-FU) every 3-4 wk during the radiation course. This clinical experience shows that many people are unable to tolerate CCRT, especially after surgery[15,16]. It is important, therefore, to develop an effective but less-toxic CCRT regimen for these patients. In this study, we conducted a non-randomized, prospective, preliminary trial to evaluate the efficacy, toxicity and tolerance of a
postoperative CCRT regimen, using weekly cisplatin as a radiosensitizer. The subsequent systemic adjuvant chemotherapy was also included in this multi-modal treatment strategy to achieve systemic control.

MATERIALS AND METHODS

Study design and subjects

Between July 1999 and June 2002, patients with T3 to operable T4, N0/N1, and M0 thoracic esophageal cancer (TNM system[10]), were prospectively enrolled. Patients with adenocarcinoma of the esophagus were excluded from this study. Experienced pathologists diagnosed all the cancers as squamous cell carcinoma. None of the patients had any prior treatment for their cancer. Written informed consent was obtained from each subject, and the study protocol was reviewed and approved by the institutional review board of studying institutes.

Pre-treatment evaluation included a complete history, physical examination, assessment of ECOG performance status, serum chemistry profile and complete blood cell count, chest radiography, echocardiogram, endoscopy with biopsy, esophagogram with barium enhancement, endoscopic ultrasound, computer tomography, and abdominal ultrasonography. All patients were informed with respect to the differences between the two arms of treatment prior to surgery. This briefing included consideration of adjuvant therapy for the very probable advanced status, the benefits of adjuvant therapy, and unpredictable benefits or side effects from chemotherapy during CCRT. The patients were then non-randomly assigned to a treatment group by a central coordinated office composed with a multi-disciplinary team including chest surgeons, radiation oncologists, medical oncologists, gastroenterologists, and nutritionists after their eligibility was established. Patients were assigned to a treatment group. Grouping was done by cross-referencing.

Surgical intervention

The surgical procedures generally consisted of right-sided thoracotomy for en bloc esophagectomy followed by abdominal and left cervical approach for reconstruction of the esophagus using proximal gastrectomy and gastroesopahgestomy via the extraperitoneal retrosternal route. En bloc resection defined sub-total resection of the esophagus along with bilateral 10-cm margin adjacent soft tissue, including all tissue behind superior vena cava, pericardium, and inferior vena cava, medial to aorta andazygous vein, and in front of the spine. For the upper third tumors, lowest 4-cm margin was accepted in order for later reconstruction. Abdominal dissection included removal of proximal one-third of the stomach, greater omentum, lymph nodes in the porta hepatic around the celiac axis, and retro-peritoneal lymph node-bearing tissue. Only sampling of cervical lymph nodes was done for all patients. All patients underwent remedial resection with a margin negative for malignant cells. Feeding jejunostomy and subclavian venous-access catheters were placed in all patients, as needed, for post-operative nutrition support and replacement of oral drug administration, respectively. All consenting patients were eligible for study if: ECOG performance status<2; serum albumin ≥30 g/L; serum creatinine level<15 mg/dL; absolute neutrophil count ≥2 000 cells/µL; and platelet count>10 000/µL. Patients who did not fulfill these criteria were excluded from the study.

Treatment protocol

Adjuvant therapy, consisting of either CCRT or radiotherapy (RT) alone, was begun 2-3 wk after surgery. RT for both groups was delivered by linear accelerator (Clinac® 1800; Varian Associates, Inc, CA) at 6 MV at 320 cGy/min. The initial 40 Gy dose was administered using a conventional appositional two-way technique, followed by a boost of 15-20 Gy using a 3D conformal treatment planning system (Clinac® 600C; Varian Associates Inc, CA). RT was delivered at 1.8 Gy/day for five consecutive days in a given week. Patients lay supine on a customized alpha cradle, with the tumor volume and surrounding nodes included within the RT field with longitudinal and lateral margins of 5 and 3 cm, respectively. The spinal cord dose was limited to 45 Gy.

In addition to RT, the CCRT group received concurrent chemotherapy consisting of six weekly doses of cisplatin (CDDP) (30 mg/m² intravenous injection over 2 h, with adequate hydration, mannitol and anti-emetic drugs) completed approximately 1 h prior to RT in the outpatient department. Adjuvant chemotherapy consisted of four monthly cycles of CDDP (20 mg/m² per d) plus 5-FU (1 000 mg/m² per d) for five consecutive days, beginning 3-4 wk after completion of CCRT. CDDP was administered as a bolus over 30 min, simultaneously started with the 5-FU continuously infused over 16 h, with adequate hydration and anti-emetic drugs.

Dose modification

Toxicity was evaluated using the common toxicity criteria published by the National Cancer Institute[37]. Both CDDP and 5-FU were held if the absolute neutrophil count was <1 500 cells/µL or the platelet count was <75 000 cells/µL. Both chemotherapeutic agents were given at 70% of the initial dose, if the neutrophils were 1 500-2 000 cells/µL or platelets were 75 000-100 000 cells/µL. RT was held only if the neutrophil level was <1 000 cells/µL or platelets were <50 000 cells/µL. For grades 3 and 4 oropharyngeal mucositis or diarrhea, the 5-FU was held until the symptoms improved. It was then restarted at 70% of the initial dose. For grades 3 and 4 renal toxicity, CDDP was held until the creatinine was <1.5 mg/dL. It was administered at 70% of the initial dose thereafter.

Patient follow-up and patterns of failure

Patients were assessed at 3, 6 and 12 mo, and then every 6-12 mo thereafter or more often, if clinically indicated. Evaluation included clinical examination, chest radiography, computed tomography, esophagography, abdominal sonography, bronchoscopy, and nuclear whole-body bone scan. Survival was calculated from the date of surgery to the most recent follow-up contact or to the date of death. The pattern of failure was defined according to the first site of failure evidenced by follow-up examination. Local failure included recurrence of the primary tumor or metastasis to regional lymph nodes. Distant failure included metastasis to any site beyond the primary tumor and regional...
lymph nodes. After recurrence, the patients received any salvage therapy that was considered useful.

**Statistical analysis**

The two treatment groups were compared with respect to base-line characteristics, with the t-test and the χ² test used for continuous and categorical variables, respectively. Primary end-point was to assess the per-protocol patients’ improvement of overall survival benefit. Secondary end-point was designed to evaluate both the per-protocol and intent-to-treat patients’ outcome of survival. Estimation of sample size for each group was performed on the basis to detect an improvement of overall survival benefit. Secondary end-point was designed to assess the per-protocol patients’ improvement for continuous and categorical variables, respectively. Primary end-point was used for analysis of all the data. Statistical significance was assumed where P<0.05.

**RESULTS**

**Patient characteristics**

The sample population of 60 patients was evenly divided between the CCRT and RT groups. The most frequent symptom at diagnosis, present in over 90% of individuals, was dysphagia. Other common symptoms included weight loss, vomiting, choking with cough, and chest pain (demographic characteristics presented in Table 1). Both groups of patients received operation for resection of their tumor. Most of them were uneventful during the peri-operative course, except 7 patients had post-operative cervical anastomotic leakage, 4 in CCRT group and 3 in RT group.

**Treatment outcome**

Median patient follow-up at the commencement of the analysis was 18.0 mo (range 4-40). Patients in the CCRT arm received 5 580-5 940 cGy (mean 5 880 cGy). Of these 30 patients, 15 completed a full course of CDDP during the RT course, 10 had four weekly cycles of full dose CDDP, and 5 had less than four cycles of reduced-dose CDDP. All patients in the CCRT group received the planned dose of RT. After the CCRT, 15 of 30 patients completed the full course of adjuvant chemotherapy, while the others received less than four cycles at a reduced dose. The mean survival for these patients was 31.9 mo, with an estimated 3-year overall survival of 70.0%, and only nine deaths. Local regional failure occurred in 40% of the group and distant metastases in 27%.

Patients in the RT arm received 5 040-5 940 cGy of radiation (mean 5 832 cGy). Twenty-four of 30 patients received the full dose. Six patients went without full planned radiation due to poor tolerance (3/6), minor anastomotic leakage (2/6), and thoracotomy wound disruption (1/6). Mean survival time for the RT group was 20.7 mo, with a median of 11.0 mo for this arm, and 38.0 mo for those still alive at the end of the study period. The estimated 3-year overall survival was 33.7%. Local regional failure occurred in 60% of the group, and distant metastases in 57% (Table 2). The cause of death for all patients after surgery and the metastatic sites are presented in Table 3. A statistically significant difference was demonstrated comparing group survival times (P = 0.003, Figure 1).

**Variance analysis**

Multivariate factor analysis for overall survival revealed that CCRT treatment and tumor cell differentiation were significant predictors (Table 4). Significant and favorable factors for overall survival included CCRT treatment (P = 0.003, Figure 1A) and moderate-well differentiation (P<0.001, Figure 1B).

**Complications and toxicity**

The most prevalent treatment-related complications for the subjects were stricture over anastomosis (36%), chronic aspiration (33%), and pneumonia (20%). There were no CCRT-related deaths during treatment, or CT-related deaths during adjuvant chemotherapy administration. Six of the 30 CCRT patients had grade 3 hematological toxicity during

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**Table 1 Characteristics of patients**

| Characteristics                  | CCRT n (%) | RT alone n (%) |
|----------------------------------|------------|----------------|
| Gender                           |            |                |
| Male                             | 30 (100)   | 27 (90)        |
| Female                           | 0 (0)      | 3 (10)         |
| Mean age±SD (yr)                 | 59.9±10.0  | 62±6.7         |
| ECOG performance status          |            |                |
| 0                                | 18 (60.0)  | 18 (60.0)      |
| 1                                | 11 (36.7)  | 10 (33.3)      |
| 2                                | 1 (3.3)    | 2 (6.7)        |
| Tumor size±SD (cm)               | 3.7±1.0    | 4.5±0.96       |
| Location of tumor                |            |                |
| Upper-third                      | 7 (23.3)   | 2 (6.7)        |
| Middle-third                     | 19 (63.3)  | 22 (73.3)      |
| Lower-third                      | 4 (13.3)   | 6 (20.0)       |
| Mean radiation dosageSD (cGy)   | 5 880±98   | 5 832±274      |
| Histologic classification        |            |                |
| Well differentiated              | 9 (30.0)   | 7 (23.3)       |
| Moderately differentiated        | 9 (30.0)   | 10 (33.3)      |
| Poorly differentiated            | 12 (40.0)  | 13 (43.3)      |
| Pathological disease staging     |            |                |
| T3N0                             | 11 (36.7)  | 11 (36.7)      |
| T3N1                             | 4 (13.3)   | 6 (20.0)       |
| T4N0-1                           | 15 (50.0)  | 13 (43.3)      |
| T stage                          |            |                |
| T3                               | 15 (50.0)  | 17 (56.7)      |
| T4                               | 15 (50.0)  | 13 (43.3)      |
| N stage                          |            |                |
| N0                               | 22 (73.3)  | 19 (63.3)      |
| N1                               | 8 (26.7)   | 11 (36.7)      |

1 All items have been calculated with no significant difference between treatment groups with t-test for continuous variables and χ² test for categorical variables. CCRT: Surgery plus concurrent chemoradiotherapy. RT alone: Surgery plus radiotherapy alone.
adjuvant chemotherapy, which required treatment modification. In the RT group, there were two treatment-related deaths secondary to upper gastrointestinal bleeding from ulcers. These two patients had grade 3 hematological toxicity, at the time of upper gastrointestinal bleeding. Renal toxicity was less than grade 2 in both groups. The most prevalent of the non-hematological toxic effects were nausea, dermatitis and esophagitis, with the rates comparable for the two groups (Table 5).

**DISCUSSION**

In comparison to surgery followed by RT alone, surgery with CCRT was associated with longer survival and higher 3-year survival rate. This not only corresponds with the findings of previous non-surgical randomized trials [7,8], but it is also in line with the outcome reported for post-operative combined modality treatment [4,5,15,21]. Most of our patients receiving CCRT had promising outcomes accompanied with acceptable and tolerable toxicity.

In the past, the overall 3-year reported survival rate for esophageal cancer remained below 35%, despite treatment with aggressive resection alone [15,22,23]. The outcome of locally advanced esophageal cancer is even less favorable, however, with no survivors from two samples of patients with either residual microscopic or macroscopic disease with single-modality treatment at 5 years [24-26]. In the study of

**Table 2** Treatment outcome

|                     | CCRT (n = 30, %) | RT alone (n = 30, %) |
|---------------------|------------------|---------------------|
| 3-yr survival       | 70.0             | 33.7                |
| Local recurrence    | 40.0             | 60.0                |
| Distant metastasis  | 27.0             | 57.0                |

**Table 3** Status after surgery and causes of death

|                                | CCRT (n = 30) | RT alone (n = 30) |
|--------------------------------|---------------|-------------------|
| Alive at last follow-up        | 21            | 11                |
| Metastasis                     |               |                   |
| Lymph nodes                    | 14            | 13                |
| Regional                       | 12            | 7                 |
| Distant                        | 2             | 9                 |
| Lung                           | 3             | 3                 |
| Liver                          | 1             | 3                 |
| Bone                           | 2             | 2                 |
| Causes of death                | 9             | 19                |
| Esophageal cancer              | 7             | 12                |
| Pneumonia                      | 0             | 2                 |
| Cardiovascular disease         | 1             | 2                 |
| Gastrointestinal bleeding      | 1             | 2                 |
| Hepatic failure                | 0             | 1                 |

1Three patients had both regional and distant nodal metastases.

**Table 4** Cox multivariate analysis

| Characteristics         | Patient number | P     | Hazard ratio (95% CI) |
|-------------------------|----------------|-------|----------------------|
| Adjuvant therapy        |                |       |                      |
| RT vs CCRT              | 30             | <0.001| 5.83 (2.36–14.43)    |
| Cell differentiation    |                |       |                      |
| Poor vs Well/moderate   | 25             | 0.001 | 5.88 (2.08–16.93)    |
| Tumor size              |                |       |                      |
| ≤4.1 cm vs >4.1 cm      | 30             | 0.058 | 2.68 (0.97–7.43)     |
| Age (yr)                |                |       |                      |
| ≤61.7 yr vs >61.7 yr    | 28             | 0.480 | 1.34 (0.60–2.99)     |
| Nodal status            |                |       |                      |
| Yes vs No               | 41             | 0.060 | 2.71 (1.00–7.38)     |
| T status                |                |       |                      |
| T4 vs T3                | 28             | 0.532 | 1.47 (0.44–4.92)     |

CI: confidence interval.

**Table 5** Toxicity assessment

|                       | CTC grades CCRT/RT |
|-----------------------|--------------------|
|                       | 0    | 1    | 2    | 3    | 4    |
| Renal toxicity        | 21/26| 9/4  | 0/0  | 0/0  | 0/0  |
| Anemia                | 21/19| 3/6  | 1/2  | 5/3  | 0/0  |
| Leukopenia            | 20/23| 5/5  | 5/2  | 0/0  | 0/0  |
| Thrombocytopenia      | 25/26| 0/0  | 4/2  | 1/2  | 0/0  |
| Nausea, vomiting      | 3/6  | 14/14| 12/10| 0/0  | 0/0  |
| Esophagitis/mucositis | 10/15| 15/8 | 5/7  | 0/0  | 0/0  |
| Dermatitis            | 9/14 | 13/11| 8/5  | 0/0  | 0/0  |
| Pneumonitis           | 25/22| 5/7  | 0/1  | 0/0  | 0/0  |
| Stenosis              | 24/20| 6/10 | 0/0  | 0/0  | 0/0  |

**Figure 1** Kaplan–Meier curves for overall survival as a function of treatment group. P value is 0.003 (A); Kaplan–Meier curves for overall survival as a function of squamous cell differentiation state (B).
Further, Herskovic

Although the Japanese Esophageal Oncology Group from esophageal cancer is widespread dissemination. by adjuvant chemotherapy resulted in a better 3-year survival This is in line with our results, where weekly CCRT followed

Rice

However, a few investigators have reported that adjuvant therapy may be beneficial after resection[4,5,15]. The role of chemotherapy and radiotherapy for locally advanced esophageal cancer still needs to be assessed. Teniere et al., have reported that post-operative RT improved local control in their sample, although it did not increase survival[27]. Rice[15] and Saito[21] have reported a significant survival advantage with adjuvant CCRT compared to adjuvant RT. This is in line with our results, where weekly CCRT followed by adjuvant chemotherapy resulted in a better 3-year survival than adjuvant RT alone.

The efficacy of adjuvant chemotherapy has been tested in this investigation because the principal cause of death from esophageal cancer is widespread dissemination. Although the Japanese Esophageal Oncology Group found no survival benefit from two cycles of adjuvant chemotherapy containing cisplatin and vindesine in their 1993 study[28], several years later they reported that two cycles of cisplatin and 5-FU after curative resection improved survival and decreased the incidence of distant and regional-node metastasis[29]. In the current study, four cycles of adjuvant chemotherapy were added to CDDP and 5-FU because the low weekly dose of CDDP during CCRT was included for its local radio-sensitizing effect rather than as systemic therapy. As only 27% of the patients in this arm of the study subsequently developed distant metastases compared to 57% in the RT arm, it seems reasonable to suggest that systemic adjuvant chemotherapy has a role in controlling distant metastasis. For the causes of death, it seemed a higher rate of non-cancer-related death in the RT groups, but most of the non-cancer-related causes were still from poor control of the tumor, local recurrence or distant metastasis. CCRT can get better control of the tumor and related death.

An important concern in CCRT is treatment toxicity. Although combined modality therapy improves outcome, it was reported to be associated with a higher incidence of toxicity. Coia et al., have reported a 56% incidence of moderate-severe acute toxicity with combined treatment[30]. Further, Herskovic et al., found that CCRT-treated patients had a higher incidence of acute grade 3 (44% vs 25%) and acute grade 4 toxicities (20% vs 3%) compared with RT alone[31], with only 50% of their sample completing all four cycles of chemotherapy. It may be that the concurrent use of 5-FU and RT in those studies caused significant mucositis and myelosuppression. To reduce toxicity while preserving the radio-sensitizing effect of chemotherapy, we excluded the radiosensitizing effect of chemotherapy, we excluded 5-FU from the CCRT regimen and used low-dose cisplatin instead. Cisplatin is considered one of the agents most active against esophageal cancer, with single-agent response rate consistently 20% or more[31]. Most of our patients were able to tolerate this regimen during CCRT, with over 80% receiving more than four doses of weekly CDDP during radiotherapy and half tolerating a full course of adjuvant chemotherapy. The only grade 3 or 4 toxicity that occurred was hematological, however, it only affected relatively few patients (20% and 17% in the CCRT and RT group, respectively). Nausea, dermatitis and mucositis of the mouth, pharynx and esophagus were common, but tolerable and reversed after supportive care. Significant renal toxicity was not noted.

To our knowledge, there were no randomized reports that explored the effects and toxicity of post-operative CCRT. One pitfall of the current study is some of the patients receiving adjusted dosage of adjuvant therapy. However, it was for the safety of the patients. From the review of articles, we learned that uniform adjuvant treatments without individualized adjustment would sometimes do harm for patients[32]. Besides, another drawback of current study was non-randomized comparison. Some potential and unmeasured factors that might have influenced patient selection were subjective ones, such as vigor, mental status, ability to cooperate with and consent to treatment protocols, referral and physician bias, and the unblended nature of the treatments. During the process of grouping, our central office had attempted to assign patients through cross-referencing method to avoid selection bias as much as possible. In conclusion, this trial implies the result of superior outcome and reduced toxicity with this combination regimen. Another large-scale randomized, double-blinded clinical trial is in progress to verify the results of this study.

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