Treatment Results of Esophageal Cancer by Different Treatment Modalities

CHIH-CHIECH HSU  CHIU-YEN LIN  LING-MIAN LIN  CHIEN-HONG LIU  TUNG-HAO CHANG

Department of Radiation Oncology, Changhua Christian Hospital

Esophageal cancer is a malignant gastro-intestinal cancer with lower curable chance. The combined modalities of treatment such as concurrent chemoradiation (CCRT) or adjuvant radiotherapy after operation (OP+R/T) was recommended recently. In this study, the treatment outcome of patients with different stages of esophageal cancer that were treated by different methods was analyzed. These data will help establishing a treatment plan on the basis of scientific evidence.

From January 2000 until December 2002, 71 patients had biopsy proven carcinoma of the esophagus (all were squamous cell carcinoma), received primary definite treatment in our hospital. Thirteen patients received radiotherapy (R/T) alone, 37 patients received CCRT, and 21 patients underwent surgery followed by adjuvant radiotherapy (OP+R/T). The survival rate and local control rate were analyzed by Kaplan-Meier method and log-rank test to determine the difference of treatment outcome between groups. Cox regression method was used for multivariate analysis of different independent factors, which might influence survival rate and local control rate.

The 2-year survival rates of stage II, III, and IV diseases were 37.5%, 28.2% and 0%, respectively (log-rank test p < 0.001). The 2-year survival rates of R/T, CCRT, and OP+R/T groups in stage II and III patients were 0%, 35.4%, and 39.1%, respectively (log-rank test p = 0.16). The multivariate analysis did not show any significant factors when calculated stages and different treatment groups. Only the status of local control influenced survival rate significantly (Cox regression p = 0.001). The 2-year local control rates of R/T, CCRT, and OP+R/T were 0%, 36.7% and 67.0%, respectively (log-rank test p < 0.001). There was an interesting finding that increasing dose of radiotherapy more than 60 Gy led to decrease the survival in CCRT group. The patients who were treated by radiotherapy less than 60 Gy had higher 2-year survival rate of 71.4% than those treated with more than 60 Gy radiation (2-year survival rate: 10%) (log-rank test p = 0.004).

CCRT and OP+R/T for the treatment of esophageal cancer would achieve better survival rate and local control than R/T alone.

Key words: Combined radiotherapy / Chemotherapy; Esophageal neoplasm; Esophageal, surgery; Esophagus, therapeutic radiology

Esophageal cancer is a malignant gastro-intestinal cancer with lower curable chance. The results of surgery or radiotherapy (R/T) treatment are disappointing with the median survival being less than 10 months and the 5-year survival rate being only 10% or less.

Since the treatment outcome of single treatment modality is poor, the combined treatment modalities, such as concurrent chemoradiation (CCRT) or adjuvant radiotherapy after operation (OP+R/T) are recommended recently. It was reported that the 2-year survival rate of esophageal cancer was around 25% and the median survival duration was around 13 months after treatment with CCRT [1]. Thus, CCRT was gradually adopted for patients with esophageal cancer as the treatment of choice in our hospital in recent 3-4 years. Of course, Op+R/T for resectable esophageal cancer was still another feasible treatment if there is no surgical contraindication. Both CCRT and OP+R/T were suggested as alternative primary treatment methods for localized (M0) esophageal cancer in National Comprehensive Cancer Network.
(NCCN) treatment guideline. Besides, the improvement of R/T technique such as three-dimensional conformal radiotherapy (3DCRT) may provide a better tumor dose distribution, thus may increase local control as compared to the conventional R/T.

In this study, the treatment outcome of patients with different stages of esophageal cancer that were treated by different methods was analyzed. This will provide us the information, based on which we can deliver more effective therapy to patients.

**MATERIALS AND METHODS**

**Patients**

From January 2000 until December 2002, 71 patents had biopsy proven carcinoma of the esophagus (all were squamous cell carcinoma) and received primary definite treatment in our hospital, were included in the study. Those patients with double cancer and patients who had recurrent cancer were excluded from analysis. The eligible patients were divided into 3 groups according to the treatment plans after retrospective review of all treatment records. The follow-up duration was from 2 to 39 months (average 12.3 months).

Radiotherapy (R/T) alone: 13 patients received R/T only to their primary tumor and regional lymph nodes.

CCRT: 37 patients received R/T and C/T simultaneously. R/T and C/T were started within the same week. The C/T was given around two courses during the course of R/T and would be further given 2-3 courses after completion of the whole course of R/T.

OP+R/T: 21 patients with resectable tumors received total or subtotal esophagectomy and regional lymph node dissection. Adjuvant R/T to the tumor bed and nodal baring area was performed after healing of the operative wound.

The AJCC 2002 staging system (Table 1)[2] was adopted in this study. The basic data of all patients were summarized at Table 2.

**Treatment**

Megavoltage linear accelerator was used to cover the primary tumor bed with 5-cm margin upward and downward the tumor. The conventional setting of R/T usually contained 2 anterior and posterior isocentric fields with dose delivery up to 39-45 Gy / 1.8-2.0 Gy daily. Then, suitable spinal cord shielding or oblique fields off spinal cord would be arranged for further treatment to avoid more than 40-45 Gy delivered to spinal cord. Recently, 3DCRT with multi-direction fields to avoid spinal cord or other critical organs has been used at the beginning of treatment or after 20-40 Gy of conventional treatment of anterior and posterior fields. This technique would provide more adequate dose to mediastinum instead of using traditional spinal cord shielding that might lead to deliver suboptimal dose to mediastinum. In addition, more precise dose of radiation was delivered to the tumor and regional lymph node. Furthermore, the dose-volume data of normal tissue might be available. The median total dose of R/T, CCRT, and OP+R/T were 64.8 Gy, 61.2 Gy, and 50.4 Gy, respectively.

In CCRT group, 4 to 5 courses of fluorouracil (1000 mg /m$^2$ of body-surface area/day) were administered as a continuous intravenous infusion for the first four days of weeks 1, 5, 9, 13, and 17. Cisplatin (75 mg/m$^2$) was given on the first day of each course.

In OP+R/T group, total or subtotal esophagectomy plus mediastinal lymph node dissection and esophagogastronomy was performed. Adjuvant R/T to primary tumor bed and lymph node might be postponed until recovery of surgical wound and general condition.

**Statistics**

The survival rate and local control rate were calculated by Kaplan-Meier method with log-rank test to detect the difference between groups. Cox regression method was used for multivariate analysis of different independent factors, which may influence survival and local control. The start point was set at the beginning of treatment to the end of follow-up, which is the last day of treatment or the day of death for those who died before the end of follow-up.
of treatment. The end point was death on survival analysis and the detection of local recurrence on local control analysis.

RESULTS

Figure 1 demonstrated the survival curves of patients at each stage after treatment. The survival results were summarized in Table 3. In general, the more advanced stage of patient was, the worse survival of patient was. The 2-year survival rates of stage II, III, and IV were 37.5%, 28.2% and 0%, respectively (log-rank test p < 0.001). However, there was no statistical significance when we compare survival between stage II and III diseases (log-rank test p = 0.54).

Because of the very poor prognosis and incurable nature of the stage IV disease in 28 patients, the stage II and III diseases in the remaining 43 patients were considered as possibly treatable diseases and were analyzed for treatment outcome. As shown in Table 4, the 2-year survival rates of R/T, CCRT, and OP+R/T groups were 0%, 35.4%, and 39.1%, respectively. It showed that CCRT and OP+R/T had better survival than R/T group but there was no statistical significance (log-rank test p = 0.16). However, univariate comparison of survival between treatment groups (R/T vs. CCRT, CCRT vs. OP+R/T, and R/T vs. OP+R/T) were performed. There was statistical significant difference between R/T and OP+R/T (log-rank test p = 0.007). In contrast, there was no statistical significant difference between R/T and CCRT (log-rank test p = 0.43), and between CCRT and OP+R/T (log-rank test p = 0.52). The multivariate analysis did not show any significant factors when analyzed by stages and treatment groups. Further multivariate analysis of adding the factor of local control status to stages and treatment groups was performed. It showed only the local control status significantly influenced survival (Cox regression p = 0.001). Thus, the patients who achieved local control after treatment had 1-year and 2-year survival rates of 41.0% and 13.7% at 1 year and 2 years after treatment (log-rank test p < 0.001).

Since the local control status had greater effect on the survival rate in this study, we further analyzed the data in greater details. The success rates of local control of esophageal cancer in different treatment groups were shown in Table 5. The 2-year local control rates of R/T, CCRT, and OP+R/T were 0%, 36.7%, and 67.0%, respectively (log-rank test p < 0.001). When taking stages and treatment groups as factors for multivariate analysis of local control, it showed statistically significant difference between CCRT group and R/T group (Cox regression p = 0.01), and between OP+R/T group and R/T group (Cox regression p = 0.01). However, stages (Cox regression p = 0.38) and the difference of local control between CCRT and OP+R/T (Cox regression p = 0.93) were not statistically significant.

Table 6 compared the survival rates and local control rates between conventional radiotherapy and 3DCRT in CCRT groups. The 2-year survival rate and 2-year local control rates of 3DCRT were 23.2% and
Table 6. Survival rates and local control rates of stage II and III patients receiving conventional radiotherapy and 3DCRT in CCRT group

<table>
<thead>
<tr>
<th></th>
<th>Conventional R/T</th>
<th>3D R/T</th>
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<tbody>
<tr>
<td></td>
<td>( N = 4 )</td>
<td>( N = 14 )</td>
</tr>
<tr>
<td>1-year survival</td>
<td>75</td>
<td>38.7</td>
</tr>
<tr>
<td>2-year survival</td>
<td>0</td>
<td>23.2</td>
</tr>
<tr>
<td>1-year local control</td>
<td>75</td>
<td>32.6</td>
</tr>
<tr>
<td>2-year local control</td>
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<td>32.6</td>
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<tr>
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<th>( \leq 60 \text{ Gy} )</th>
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<tr>
<td></td>
<td>( N = 7 )</td>
<td>( N = 11 )</td>
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<tr>
<td>1-year</td>
<td>85.7</td>
<td>20.2</td>
</tr>
<tr>
<td>2-year</td>
<td>71.4</td>
<td>10</td>
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\( p < 0.001 \)

Table 7. Survival rates of stage II and III patients receiving different dose of R/T in CCRT group

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<th></th>
<th>( \leq 60 \text{ Gy} )</th>
<th>&gt; 60 Gy</th>
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<tbody>
<tr>
<td></td>
<td>( N = 7 )</td>
<td>( N = 11 )</td>
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<tr>
<td>1-year</td>
<td>58.3</td>
<td>47.4</td>
</tr>
<tr>
<td>2-year</td>
<td>100</td>
<td>62.4</td>
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\( p = 0.54 \)

Table 8. Distant metastatic rates in different treatment groups

<table>
<thead>
<tr>
<th></th>
<th>R/T</th>
<th>CCRT</th>
<th>OP+R/T</th>
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<tbody>
<tr>
<td>1-year</td>
<td>58.3</td>
<td>47.4</td>
<td>32.3</td>
</tr>
<tr>
<td>2-year</td>
<td>100</td>
<td>62.4</td>
<td>50.7</td>
</tr>
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\( p = 0.54 \)

DISCUSSION

In general, R/T alone was given when lesions are deemed inoperable because of extensive tumor invasion or surgical contraindications in the past. Earlam and Cunha-Melo [3] reviewed 49 series including more than 8400 patients treated primarily with R/T. They found overall survival rate at 1, 2, and 5 years was 18%, 8%, and 6%, respectively. Our results for R/T group also may not be satisfactory. The 1- and 2-year survival rates were only 50% and 0%, respectively.

Earlam and Cunha-Melo [4] reviewed 122 series including more than 83000 patients treated primarily by surgery. The overall 5-year survival rate for patients with resectable tumor was 12%. Thus, postoperative R/T for enhancing treatment outcome was generally used for our patients with T3 or T4 tumors (even surgical margin was clear). Drucker and co-workers [5] reported 23 of 45 patients treated with 40-60 Gy of radiotherapy postoperatively. At 3 years, those patients had survival rate of 20%. There were comparable results for 2-year survival rate and local control rate of our OP+R/T group (39.1% and 67.0%) in our study.

A number of investigators have used CCRT for the primary treatment of esophageal cancer [1,6]. Our study demonstrated the 2-year survival and local control rates of 35.4% and 36.7%, respectively, that were higher than those of R/T as shown in Table 4 and 5 (statistically significant difference for the local control group). Arnold and co-workers [3] reported a famous randomized research of RTOG 85-01 trial in NEJM. They evaluated the efficacy of 4 courses of combined fluorouracil and cisplatin plus 50 Gy of R/T, as compared with 64 Gy of radiotherapy alone, in patients with localized thoracic esophageal cancer. The patient treated by CCRT had 2-year survival rate of 38%, whereas the patients treated by R/T alone had 2-year survival rate of 10% (\( p < 0.001 \)). Forty percent of the patients who received R/T had persistent disease and 24% had local recurrences, as compared with those who received CCRT was 27% and 16%, respectively (\( p < 0.01 \)). CCRT of 50 Gy had superior results to R/T of 64 Gy both in survival and local control rates. The above findings would suggest that CCRT rather than R/T alone as the primary treatment for
localized esophageal cancer would result in better outcome. In our study, the 2-year survival rate of CCRT group was similar to that of OP+R/T (around 35-40%). Thus, CCRT might be another alternative treatment choice for patients with localized esophageal cancer who hesitated or were not suitable for operation.

The use of 3DCRT was a recent effort for us to provide better dose distribution in esophageal mass. However, it did not show significant superiority to conventional radiotherapy in CCRT group (Table 6). This might be due to our small case number or short-term follow-up duration. There might be surprising survival results of dose escalation more than 60 Gy with inferior therapeutic results to those of less than 60 Gy in our CCRT group. In addition, the similar findings were also reported by Radiation Therapy Oncology Group (RTOG) 94-05 phase III trial [6]. In that study, 236 patients with M0 esophageal cancer were randomized to receive combined-modality therapy consisting of 4 monthly cycles of fluorouracil and cisplatin with concurrent 64.8 Gy versus the same C/T schedule but with concurrent 50.4 Gy. In that study, authors reported a better 2-year survival rate of 40% in 50.4 Gy CCRT group than that of 31% in 64.8 Gy CCRT group (no statistical significant difference). They also concluded that dose escalation in CCRT might not be better than the standard dose of CCRT although the reason was not clear.

There were 2 patients with severe radiation pneumonitis in our CCRT group. Both of them received 3DCRT with treatment dose of 64.8 Gy and 70.2 Gy, respectively. Literature was searched for the possible tolerated dose of normal lung tissue. In Washington University, Mary VG and co-workers [7] studied the significant predictors of severe pneumonitis after evaluation of 99 patients with lung cancer who were treated by 3DCRT. They found that the percentage of normal lung volume which received dose more than 20 Gy ($V_{20}$) would be an independent factor for predicting severe radiation pneumonitis in a multivariate analysis including factors of $V_{20}$, maximum lung dose, mean lung dose, effective volume, and primary tumor location. They reported 8% of patients with $V_{20}$ between 22-31% developed severe pneumonitis. One patient with fatal pneumonitis occurred in $V_{20}$ range at 32-40%, and the other three patients with fatal pneumonitis occurred in $V_{20}$ more than 40%. They concluded that it might have very low risk of pneumonitis when the $V_{20}$ was below 25%. Besides, all fatal pneumonitis occurred with a $V_{20} \geq 35\%$ in their study. The above findings were used for reevaluation of the patients with severe pneumonitis in our study.

There were 48% and 35% of $V_{20}$ noted in the two patients with severe pneumonitis. Thus, we may have a reference point for prevention of severe pneumonitis in our 3DCRT from our study. We may keep $V_{20}$ below 25% as possible in our 3DCRT through the efforts of lowering down the weighting dose of beam that may injure lung, and/or reducing the irradiated tumor margin, and/or reducing total dose when $V_{20}$ is still too high.

Combined-modality treatment for localized esophageal cancer is the major option currently. The optimal arrangement of operation, chemotherapy, and radiotherapy may need further investigation to achieve better results for patients with esophageal cancer.

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REFERENCE

以不同方式治療食道癌之成果報告

許智捷  林秋燕  林玲綸  劉建鴻  張東浩
彰化基督教醫院  放射腫瘤科

食道癌是一種較惡性且治癒率差之癌症，其所使用之治療方式通常為合併化學及放射治療，或是根治性手術後加輔助性之放射治療。

此篇研究統計自2000年1月至2002年12月共七71例病人經病理報告證實為食道扁平上皮細胞癌，且在本院接受根治性之治療者，13例病人僅接受放射治療，37例病人接受合併化學及放射治療，21例病人接受手術加輔助性放射治療。使用Kaplan-Meier方式統計其存活率及局部控制率，並分別以log-rank test及Cox regression作為單變數及多變數分析不同因素是否對存活率及控制率造成明顯差異。

第二、三、四期病人之兩年存活率分別為37.5%、28.2%、及0%，其log-rank test p < 0.001具明顯統計差異。針對第二及三期使用放射治療、合併化學及放射治療、手術加放射治療之兩年存活率分別為0%、35.4%、39.1%，其log-rank test p = 0.16不具統計差異。以多變數因子分析癌症期別、治療方式、是否達到局部腫瘤控制對存活率之影響，僅發現有局部控制之病人具有顯著較好之存活率（Cox regression p = 0.001）。第二及三期使用放射治療、合併化學及放射治療、手術加放射治療之兩年局部控制率分別為0%、36.7%、67%（log-rank test p < 0.001）。

針對沒有遠端轉移之食道癌患者，使用合併化學及放射治療或手術後加輔助性放射治療，較只使用放射治療，有較好之存活率及控制率。

關鍵詞：合併化學及放射治療；食道腫瘤；食道；手術治療；食道；放射治療