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Original Article

# Feasibility of intensity-modulated radiotherapy for esophageal cancer in definite chemoradiotherapy

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**Abstract**

*Background*: Esophageal cancer is a highly lethal malignancy, and its treatment has undergone a major evolution over the past 15 years. The objective of this study was to report our experience on the efficacy of definite chemoradiotherapy with the intensity-modulated radiotherapy (IMRT) technique in treating locally advanced esophageal cancer.

*Methods*: From September 2004 to November 2011, 39 patients with biopsy-proven esophageal cancer, clinical stage T1-4N0-3M0 according to the American Joint Committee on Cancer 7th edition were enrolled. In these enrolled cases, either the tumor was unresectable or the patients refused surgery. All patients received a total radiation dose of 40−56 Gy in 20−28 fractions using IMRT planning. Five to seven radiation beam angles were designed according to the specific shape of the clinical target volume (CTV) and were delivered by a linear accelerator with photons of 6−10 MV energy. The gross tumor volume, CTV, planning target volume, and the organs at risk were outlined, and the homogeneity index (HI) and the conformity index (CI) were calculated. The treatment-related toxicities were also reviewed.

*Results*: The mean follow-up time was 22.4 months (range, 2.0−91.0 months). The 2- and 3-year overall survival rates were 30% and 28%, respectively. The most common Grade 3/4 toxicity was hematologic toxicity (43.6%). The IMRT plans showed high-dose homogeneity to the target, with a calculated HI of 0.9. The calculated CI of 0.8 also showed high conformity treatment dose to target within an acceptable dose range. For the total lungs, the average mean dose was 1313.7 cGy. The V5 and V20 of the total lungs were 67.8% and 23.4%, respectively. For the heart, the average mean dose was 2319.2 cGy. The V30 and V35 of the heart were 30.2% and 21.5%, respectively.

*Conclusion*: Concurrent chemoradiotherapy using the IMRT technique for treating locally advanced unresectable esophageal cancer is feasible, with better conformity of target volume as well as improved sparing of organs at risk.



*Keywords:* chemoradiotherapy; esophageal carcinoma; intensity-modulated radiotherapy

## 1. Introduction

Esophageal cancer is a highly lethal malignancy, and its treatment has undergone a major evolution over the past 15 years. Surgical intervention is the treatment of choice for early stage esophageal cancer, but the 5-year survival rates reported in a recent study were about 15−20% for surgery alone.[1] For potentially resectable locally advanced tumor stages, trimodal treatment including neoadjuvant chemo-radiotherapy followed by surgical resection showed better

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survival benefit than surgery alone. However, about 30−40% of these patients are not suitable for surgery due to technical, functional, or medical reasons.[2]

Definitive chemoradiotherapy is an alternative treatment option for patients who are not candidates for surgery. The landmark trial of definite chemoradiotherapy is the Radiation Therapy Oncology Group (RTOG) 85-01, which showed a better 5-year survival rate than radiation alone and a projected 10-year survival rate of 20%.[3,4] Locoregional recurrence is the most common failure pattern of definite chemoradiotherapy, but dose escalation to more than 50.4 Gy did not show any benefit according to a report by Minsky et al.[5]

Radiotherapy is a major treatment component for unresectable locally advanced esophageal carcinoma. Traditionally, the radiation technique is arranged with an anteroposterior/posteroanterior field, followed by the three-field technique with an anteroposterior field plus two posterior oblique fields or the four-field box technique. There have been a number of advances in treatment planning and delivery in radiotherapy, and the current recommended planning method of choice is three-dimensional-conformal radiotherapy (3D-CRT).[6]

The innovative technology of intensity-modulated radiotherapy (IMRT) in radiation delivery offers improved coverage of the target volume while reducing the doses delivered to the surrounding normal tissues. IMRT is an advanced form of 3D-CRT, which uses nonuniform radiation beams to maximize the radiation dose of the target volume and simultaneously minimize the radiation dose of normal tissues. The introduction of IMRT for treating many malignancies, such as malignant cancers of the head and neck, prostate, breast, ovary, cervix, and lung, allowed for reduced toxicities without sacrificing local control rate.

There are several critical organs surrounding the esophagus, such as the lung, the heart, and the spinal cord, which makes it difficult to achieve better local control by dose escalation using the conventional radiation technique. The better dosimetric characteristics of IMRT are thought to provide a better dosimetric profile, thereby reducing the treatment-related toxicities when used concurrently with chemotherapy for unresectable esophageal cancer.

In this paper, we present our experience of definite chemoradiotherapy with the IMRT technique in treating locally advanced esophageal cancer.

## 2. Methods

### 2.1. Patient population and concurrent chemotherapy

Between September 2004 and November 2011, 39 patients with locally advanced esophageal cancer who received definite chemoradiotherapy with the IMRT technique were retrospectively reviewed. All patients had biopsy-proven adenocarcinoma or squamous cell carcinoma of the esophagus. The clinical stage screening tools included chest computed tomography (CT), endoscopic ultrasound, chest X-ray, bone scan, liver sonography, and/or positron emission tomography/CT (PET/CT) scan. According to the American Joint Committee on Cancer (AJCC) TNM staging 7$^{th}$ edition, patients who had clinical stage T1-4N0-3M0, had inoperable esophageal cancer, or refused operation for esophageal cancer were included in the study.

The median age was 58 years (range, 40−84 years). Most patients were men, and nearly all patients had squamous cell carcinoma, except one who had adenocarcinoma. The tumor location was mainly in the middle thoracic esophagus (46.2%), followed by the lower thoracic esophagus (28.2%). Twenty-nine patients (74.4%) had a clinical tumor stage of more than AJCC Stage IIIA. The details of patients' characteristics are presented in Table 1.

The concurrent chemotherapy consisted of intravenous cisplatin (20 mg/m$^2$) for 1 hour and continuous intravenous infusion of fluorouracil (5-FU; 800 mg/m$^2$) for 24 hours from Day 1 to Day 4 on Week 1 and Week 5 during radiotherapy for

Table 1
Patient and tumor characteristics, radiation dose, and clinical response after treatment ($n$ = 39).

| Variables | $n$ | % |
|---|---|---|
| *Sex* | | |
| Women | 2 | 5.13 |
| Men | 37 | 94.87 |
| *Eastern Cooperative Oncology Group performance status* | | |
| 1 | 5 | 12.82 |
| 2 | 34 | 87.18 |
| *Histology* | | |
| Squamous cell carcinoma | 38 | 97.44 |
| Adenocarcinoma | 1 | 2.56 |
| *T stage* | | |
| T1 | 3 | 7.69 |
| T2 | 2 | 5.13 |
| T3 | 26 | 66.67 |
| T4 | 8 | 20.51 |
| *N stage* | | |
| N0 | 9 | 23.08 |
| N1 | 25 | 64.10 |
| N2 | 5 | 12.82 |
| *American Joint Committee on Cancer stage* | | |
| <IIIA | 10 | 25.64 |
| ≥IIIA | 29 | 74.36 |
| *Chemotherapy cycles* | | |
| <4 | 16 | 41.03 |
| ≥4 | 23 | 58.97 |
| *Tumor length (cm)* | | |
| <8 | 25 | 64.10 |
| ≥8 | 14 | 35.90 |
| *Tumor location* | | |
| Cervical | 2 | 5.13 |
| Upper thoracic | 8 | 20.51 |
| Middle thoracic | 18 | 46.15 |
| Lower thoracic | 11 | 28.21 |
| *Radiation dose (cGy)* | | |
| ≤5040 | 14 | 35.90 |
| >5040 | 25 | 64.10 |
| *Clinical response after chemoradiotherapy* | | |
| Complete response | 23 | 58.97 |
| Partial response | 10 | 25.64 |
| Disease progression | 1 | 2.56 |
| Unknown | 5 | 1.28 |

two cycles. Additional chemotherapy was prescribed using the same regimen with concurrent chemotherapy every 3 weeks for two to four cycles according to the patients' clinical condition and the physician's decision.

### 2.2. Radiotherapy

The radiotherapy treatment plan was performed according to the protocol described in our previous study.[7] The gross tumor volume (GTV), the clinical target volume (CTV), planning target volume (PTV), and the organs at risk were outlined on the planning CT scan images. The GTV was contoured by the attending radiation oncologist using all available resources, such as PET/CT scan, endoscopic findings, and diagnostic CT scan images. The CTV included 1.0-cm expansion of the GTV in circumferential direction, 5-cm extension of the GTV in the cephalad–caudad direction, lymph nodes at the mediastinum, supraclavicular area (for cervical, upper, and middle thoracic esophageal tumors), and celiac trunk region (for lower thoracic esophageal tumor portion). A margin of 0.5 cm was added to the CTV, given the PTV, to account for daily setup error and organ motion. We planned to deliver a total dose of 40–56 Gy to the PTV in 20–28 fractions with or without concomitant boost to the primary tumor within 5–6 weeks. Dose constraint for lungs was less than 15 Gy for mean lung dose, and for a volume under 30%, a dose of more than 20 Gy (V20) was used. Dose constraint for a heart with volume less than 30% was 35 Gy.

Five to seven radiation beam angles were designed by an experienced radiation oncologist according to the specific shape of the CTV. The radiation doses were delivered by a linear accelerator with photons of 6 MV or 10 MV energy. The quality of the plan was evaluated by dose–volume histogram, dose-distribution curves, a calculated homogeneity index (HI), and a calculated conformity index (CI). The HI was calculated and defined as the fraction of PTV with a dose between 100% and 112% of the prescribed dose. The CI was calculated with modification according to the definition proposed by Baltas et al[8] for evaluating brachytherapy implants and was defined as $CI = C_1 \times C_2$, and $C_1 = V_{CTVref}/V_{CTV}$, $C_2 = V_{CTVref}/V_{ref}$, where $V_{CTVref}$ is CTV receiving the reference dose or above, $V_{CTV}$ is the volume of CTV contouring, and $V_{ref}$ is the body volume receiving the reference dose or above.

### 2.3. Toxicity assessment

Acute toxicities were divided into hematologic toxicity (leukopenia, anemia, and thrombocytopenia) and non-hematologic toxicity (esophagitis, radiation dermatitis, and pneumonitis) according to the toxicity criteria of RTOG.[9] All patients were evaluated each week during the treatment and every 2 weeks after the last chemotherapy for at least 3 months. The physical examinations and image assessment were performed every 3–4 months for 3 years and then every 6 months for 2 years. Annual follow-up was arranged for the following 5 years.

### 2.4. Treatment response evaluation

All patients received either chest CT, gastroscopy plus biopsy, or PET/CT scan 2–12 weeks after completion of radiotherapy. The treatment response was recorded and was defined as clinically complete response (CR), partial response (PR), or disease progression (PD) according to the Response Evaluation Criteria in Solid Tumors guidelines version 1.1.[10] The clinical CR was defined as no residual tumor according to the pathologic report of post-treatment gastroscopic biopsy, post-treatment chest CT, and no evidence of distant metastasis by PET/CT scan. The patients who did not have restaging examinations mentioned above or residual tumor after concurrent chemoradiotherapy (CCRT) were classified into PR or PD.

### 2.5. Treatment failures

The diagnosis of residual, recurrence, or metastasis disease was aided by clinical examinations including physical examination, CT, esophagoscopy plus biopsy, and/or PET/CT scan. The locoregional recurrent locations were compared with the treatment planning and isodose curve and were divided into in-field, marginal, and out-field failure. In- or out-field failure was assessed based on whether the failure location was inside or outside the PTV area. Marginal failure was defined as outside of PTV, but less than 1 cm in circumferential direction and 3 cm in the cephalad–caudad direction.

### 2.6. Statistical analysis

The 1st day was defined as the start day of radiotherapy. The survival was analyzed by the Kaplan–Meier method. The locoregional recurrence rate and distant metastasis rate were represented by the cumulative incidence. Cox proportional hazard models were used for the calculation of the hazard ratio of death. The differences were considered significant when the $p$ values were $< 0.05$ by log-rank test. The data were analyzed using SAS 9.3 statistical software (SAS Institute Inc., Cary, NC, USA).

## 3. Results

### 3.1. Clinical results

The mean follow-up time was 22.4 months (range, 2.0–91.0 months). For alive patients, the mean follow-up time was 53.4 months (range, 5.04–91.0 months). The 2- and 3-year overall survival rates were 30% and 28%, respectively (Fig. 1). Two patients died within 1 month after radiotherapy due to pneumonia. Six patients died between 1 month and 3 months after radiotherapy, and the main cause of death was infection (pneumonia and sepsis). Among these eight patients, four patients received post-CCRT restaging examinations. Complete clinical response was found in one patient, PR in two patients, and progression of disease in one patient. The other four patients had developed pneumonia complicated

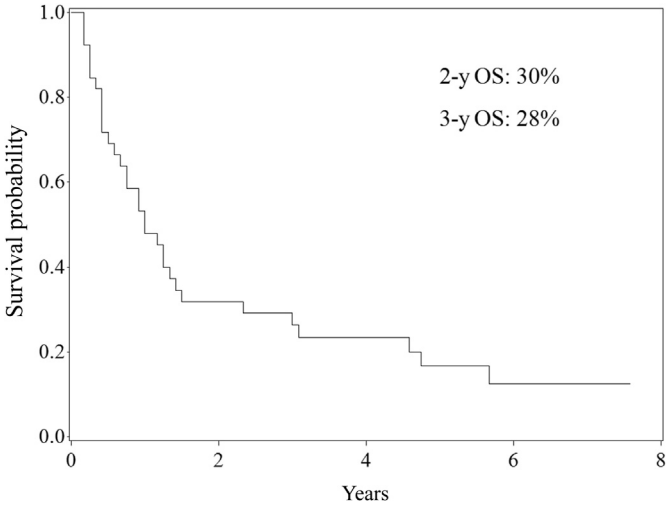


Fig. 1. Overall survival (OS).

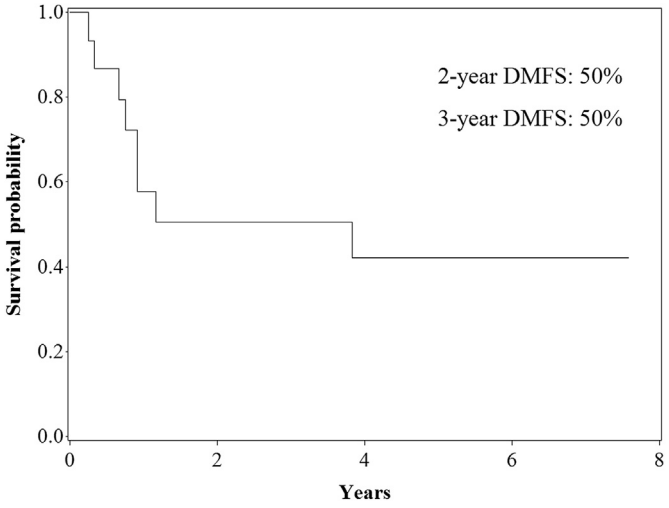


Fig. 3. Distant metastasis free survival rate (DMFS).

with respiratory failure before post-CCRT restaging examinations were arranged.

Six patients experienced locoregional recurrence, including local recurrence alone in one, regional lymph node recurrence alone in four, and both in one. Of the six patients, in-field failure was found in four, out-field failure in one, and marginal failure in one. The 2- and 3-year locoregional relapse-free survival rates were 60% and 50%, respectively (Fig. 2).

Eight patients experienced distant metastases (2 with lung, 1 with pleural seeding, 1 to brain, 1 to bone, 1 to liver, 1 to colon, and 1 with anterior mediastinal metastasis). Both the 2- and 3-year distant metastasis-free survival rates were 50% (Fig. 3).

Among all patients, 23 and 10 patients achieved CR and PR, respectively. One patient had PD, and the outcome in five patients was unknown. The overall response rate (CR and PR) was 84.6%.

Of the 23 patients who reached clinical CR, five patients (22%) experienced distant metastasis, six patients (26%) experienced locoregional relapse, and one experienced both.

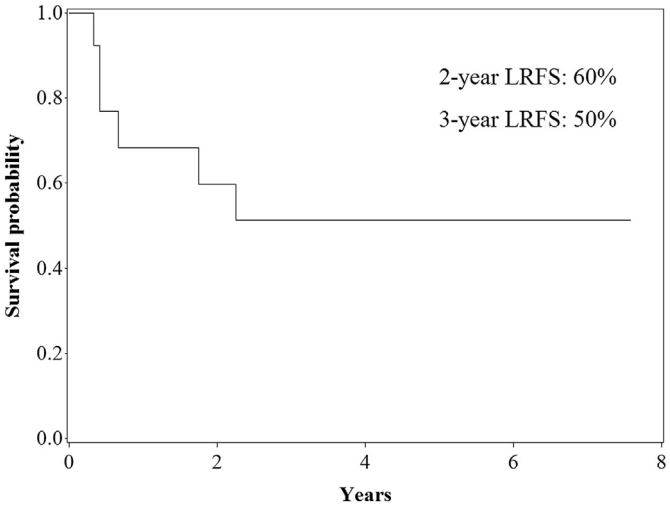


Fig. 2. Locoregional relapse-free survival rate (LRFS).

### 3.2. Treatment-related toxicities and compliance

Twenty-five patients had radiation dose of over 50.4 Gy, three patients received < 50 Gy, and 11 patients received between 50 Gy and 50.4 Gy. Twenty-three patients could tolerate chemotherapy for at least four cycles. All three patients with a radiation dose less than 50 Gy received concurrent chemotherapy for two cycles. The details of treatment-related toxicities are presented in Table 2.

The most common Grade 3/4 toxicity was hematologic toxicity (43.6%). Only one patient had Grade 4 non-hematologic toxicity (radiation dermatitis). No Grade 3/4 esophagitis or pneumonitis was found.

### 3.3. Dosimetric results

Dosimetric analysis was performed for 39 patients; the details of dose data are presented in Table 3. The IMRT plans showed high-dose homogeneity to the target, with a calculated HI of 0.9. The calculated CI of 0.8 also showed high conformity treatment dose to target within an acceptable dose range. For the total lungs, the average mean dose was 1313.7 cGy.

Table 2
Treatment-related toxicities ($n$ = 39).

| | $n$ | % |
|---|---|---|
| Hematology | | |
| Grade 0 | 4 | 10.26 |
| Grade 1 | 5 | 12.82 |
| Grade 2 | 13 | 33.33 |
| Grade 3 | 9 | 23.08 |
| Grade 4 | 8 | 20.51 |
| Nonhematology | | |
| Grade 0 | 6 | 15.38 |
| Grade 1 | 8 | 20.51 |
| Grade 2 | 24 | 61.54 |
| Grade 3 | 0 | 0 |
| Grade 4 | 1 | 2.56 |

Table 3
Dosimetric results ($n = 39$).

| | Mean | Standard deviation | Median | Minimum | Maximum |
|---|---|---|---|---|---|
| GTV (mL) | 86.04 | 97.20 | 55.30 | 0.00 | 479.50 |
| GTV mean (cGy) | 5431.79 | 933.09 | 5480.40 | 0.00 | 6054.10 |
| CTV (mL) | 418.83 | 198.88 | 374.20 | 73.90 | 1036.70 |
| CTV mean (cGy) | 5421.44 | 126.79 | 5399.40 | 5180.50 | 5739.90 |
| PTV minimal dose (cGy) | 4877.92 | 142.87 | 4912.50 | 4382.50 | 5119.50 |
| PTV maximal dose (cGy) | 5762.04 | 372.31 | 5746.10 | 3938.50 | 6221.50 |
| PTV volume (mL) | 645.42 | 264.54 | 598.00 | 268.60 | 1371.90 |
| PTV reference (%) | 0.97 | 0.02 | 0.97 | 0.89 | 1.00 |
| Body reference (mL) | 747.73 | 288.21 | 714.30 | 162.60 | 1546.90 |
| Conformity index | 0.80 | 0.05 | 0.80 | 0.68 | 0.92 |
| Homogeneity index | 0.90 | 0.08 | 0.91 | 0.71 | 1.00 |
| Total lung V5 (%) | 67.80 | 17.60 | 70.40 | 21.60 | 93.50 |
| Total lung V20 (%) | 23.41 | 7.77 | 24.90 | 8.80 | 42.70 |
| Total lung mean (cGy) | 1313.73 | 346.79 | 1319.70 | 579.80 | 2046.00 |
| Heart V35 (%) | 21.53 | 15.87 | 17.50 | 0.00 | 73.00 |
| Heart V30 (%) | 30.17 | 19.05 | 27.20 | 0.00 | 87.40 |
| Heart mean (cGy) | 2319.22 | 937.74 | 2527.20 | 67.00 | 4158.90 |

CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume.

The V5 and V20 of the total lungs were 67.8% and 23.4%, respectively. For the heart, the average mean dose was 2319.2 cGy. The V30 and V35 of the heart were 30.2% and 21.5%, respectively.

### 3.4. Multivariate analysis

In multiple variable analysis, more than four cycles of chemotherapy and complete clinical tumor response after treatment were significant predictors of survival ($p = 0.0244$ and $p = 0.0039$, respectively; Table 4).

## 4. Discussion

Five to seven beam portals, according to the specific shape of the CTV, were chosen. This portal number was in agreement with other values in the published literature.[11,12] Using IMRT in our study, the conformal index was 0.8, which showed good dose conformity for CTV. The calculated HI of 0.9 in our study also represented a good high-dose homogeneity to the target.

Table 4
Multivariate analysis ($n = 39$).

| Variables | Interpretation | Full model | | |
|---|---|---|---|---|
| | | Hazard ratio | 95% CI | $p$ |
| Age | Every 1-y increment | 1.010 | (0.979–1.043) | 0.5246 |
| Stage | ≥IIIA vs. <IIIA | 1.157 | (0.427–3.138) | 0.7740 |
| CT cycles | ≥4 vs. <4 | 0.314 | (0.115–0.861) | 0.0244 |
| Tumor length | ≥8 vs. <8 | 0.981 | (0.328–2.938) | 0.9730 |
| Tumor location | Cervical and Tu vs. Tm and Tl | 0.881 | (0.333–2.329) | 0.7987 |
| RT dose (cGy) | >5040 vs. ≤5040 | 2.164 | (0.780–6.007) | 0.1384 |
| Response | non-CR vs. CR | 4.757 | (1.649–13.724) | 0.0039 |

CI = confidence interval; CR = complete response; CT = chemotherapy; RT = radiotherapy; Tl = lower thoracic esophageal tumor; Tm = middle thoracic esophageal tumor; Tu = upper thoracic esophageal tumor.

The IMRT treatment planning system is widely used in many malignancies, such as malignancies of the head and neck, lung, and prostate, as well as in gynecological malignancies. IMRT uses nonuniform radiation beams to deliver a maximum delivery dose to the PTV and to minimize the radiation dose to the normal tissue outside the target. It allows not only better dose conformity and homogeneity but also an equivalent local control rate compared with conventional radiotherapy.

The feasibility of IMRT in esophageal cancer has also been demonstrated with homogeneity of target volume dose and decreased radiation dose to the organs at risk.[13] Retrospective studies comparing 3D conformal versus IMRT for patients with esophageal cancer showed superior dose conformity and homogeneity with IMRT and reduction of radiation dose to normal organs (the lungs and heart).[11] Our previous study also demonstrated the practicality of the use of IMRT in postoperative esophageal cancer patients, which showed a good coverage of the target and high-dose homogeneity while decreasing doses to normal tissues (the lung, heart, and spinal cord).[7]

The total lung V20 and the mean lung dose are the most common parameters in predicting the incidence of radiation pneumonitis. The incidence of pneumonitis decreased with the use of IMRT compared with 3D-CRT.[11,14] In our study, the mean doses and the average V20 of the total lungs were 1313.7 cGy and 23.4%, respectively. Compared with our previous study, the total lung V20 was higher, although it did not exceed the dose constraints.[7] This increased the proportion of total lung V20 mainly because of advanced stage and bulky tumor mass.

In previous studies, the older radiotherapy technique of two-dimensional conformal chemoradiotherapy was frequently used. Based on RTOG criteria, the RTOG 85-01 trial showed that 48% of cases had ≥ Grade 3 hematologic toxicities and 33% had ≥ Grade 3 nonhematologic toxicities (the lung and esophagus).[3] In the INT-0123 dose comparison trial, 71% of patients had ≥ Grade 3 acute toxicities and 37% of patients had ≥ Grade 3 late toxicities in the standard-dose group.[5] An increased cumulative incidence of cardiac-related death in the 3D-CRT group compared with that in the IMRT group was also reported.[15] The treatment-related toxicities in our study were fewer than that those reported in previous studies, which showed that 43.6% of patients had ≥ Grade 3 hematologic toxicity and 2.56% had ≥ Grade 3 nonhematologic toxicities.

In our study, the main cause of death was pneumonia (11/32, 34.4%), and the relationship between the radiation pneumonitis and pneumonia was reviewed. Six of the 11 patients had pneumonia patches in the radiation beam pathway and radiation pneumonitis complicated with pneumonia cannot be ruled out. Four patients had pneumonia patches out of the radiation beam pathway. One of the patients did not complete radiotherapy and was lost to follow-up without further imaging study.

In our study, six patients had locoregional recurrence. Of the six patients, four had in-field failure and received a radiation dose between 50 Gy and 50.4 Gy. The pretreatment tumor locations were as follows: two upper thoracic, two middle thoracic, one cervical, and one lower thoracic. A report published in 2012 by the MD Anderson Cancer Center found that the most common failure pattern after definite chemoradiotherapy was GTV failure, with an increased incidence associated with tumor status (T3/T4) and tumor size (> 8 cm).[16] Of the six patients who had locoregional recurrence in our study, five had clinical T3 status and one had T1. Only one patient had a tumor size of 8 cm, and the mean tumor size of the six patients was 5.95 cm.

A meta-analysis published in 2012 reported a 2-year overall survival rate between 35% and 58% after definite chemoradiotherapy.[17] In our study, the 2- and 3-year survival rates were 30% and 28%, respectively. These decreased survival rates might be due to more locally advanced stage (> Stage IIIA, 74.4%) and poor performance status (Eastern Cooperative Oncology Group performance status = 2, 87.2%). In the multivariate analysis, more than four cycles of chemotherapy and complete clinical tumor response played a statistically significant role in prediction of better survival.

In our study, the overall response rate was 84.6% using the conventional concurrent chemotherapy regimen with cisplatin and 5-FU. The response rate was better than in other published studies.[18,19] The conventional chemotherapy regimen combined with radiotherapy still appears to be effective in the treatment of esophageal cancer. However, as surgical intervention was not a component of the treatment modalities in our study, no definite evidence for pathologic CR could be evaluated.

A novel radiotherapy technique called "volumetric modulated arc therapy" (VMAT) is a more sophisticated form of IMRT and potentially offers greater sparing of normal tissues and a shorter delivery time. Recent studies showed equivalent or superior dose distribution but a significantly decreased dose to organs at risk in VMAT compared with standard step-and-shoot IMRT in esophageal cancer.[20,21] However, VMAT has the disadvantage of delivering lower doses to a greater volume of the surrounding normal tissues. Long-term follow-up data are still needed to demonstrate whether or not VMAT increases late toxicities.

There were several limitations in our study, which included the use of retrospective data, a small sample size, and possible selection bias. However, our study demonstrated that CCRT using the IMRT technique for treating locally advanced unresectable esophageal cancer is feasible, with better conformity of target volume and improved sparing of organs at risk.

In conclusion, for locally advanced unresectable esophageal cancer, CCRT using the IMRT technique provides better conformity of target volume as well as improved sparing of organs at risk. In addition, more than four cycles of chemotherapy and complete clinical tumor response after treatment were significant predictors of survival.

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