


ORIGINAL ARTICLE

Three-dimensional conformal radiation therapy alone for esophageal squamous cell carcinoma: 10-year survival outcomes

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Keywords

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Abstract

Background: Concurrent chemoradiation is the standard treatment for locally advanced esophageal squamous cell carcinoma (SCC). We conducted a phase II study to explore the effect of three-dimensional conformal radiotherapy (3-DCRT) alone for patients with locally advanced esophageal SCC. This study aimed to analyze the long-term survival outcomes.

Methods: Between November 2004 and April 2007, 30 patients with thoracic esophageal SCC underwent late-course sequential boost 3-DCRT at Fudan University Shanghai Cancer Center. The planning target volume (PTV1) comprised a 1.2–1.5 cm lateral margin around the gross tumor volume and a 3.0 cm margin, superior and inferior to the gross tumor volume. PTV2 encompassed the gross tumor volume with a margin of 0.5–0.7 cm. The PTV1 dose delivered was 50 Gy, and the PTV2 dose was a boost dose of 16 Gy, resulting in a total dose of 66 Gy. No chemotherapy was administered.

Results: The median follow-up time was 30 months for all patients, and 132 months for patients who were alive. The median overall survival was 27 months (95% confidence interval [CI] 18.9–35.0). The 2-, 5-, and 10-year overall survival rates were 56.6%, 33.3%, and 26.6%, respectively. The median progression-free survival was 14 months (95% CI 7.7–20.2 months), and the 2-, 5-, and 10-year progression-free survival rates were 33.3%, 30.0%, and 26.6%, respectively. No severe late toxicity was observed in long-term survivors.

Conclusion: Late-course sequential boost 3-DCRT is safe and feasible with promising long-term outcomes for esophageal SCC.

Introduction

Esophageal cancer is the sixth leading cause of cancer-related mortality and the eighth most common cancer in the world.¹ The estimated numbers of incident and mortality cases of esophageal cancer are 477 000 and 375 000 annually in China, respectively.² The main histological subtype of esophageal cancer is squamous cell carcinoma (SCC) in East Asia.³ The prognosis of esophageal SCC is poor; the five-year survival rate remains <20%.⁴

Concurrent chemoradiotherapy was a standard treatment for patients with locally advanced esophageal cancer;

the five-year overall survival (OS) was 14–26%.^{5–8} However, 20% of patients in the chemoradiation group had life-threatening toxicities, including 2% toxic deaths, and 32% of patients were unable to receive chemoradiotherapy as planned.⁵ Radiotherapy alone was administered widely for esophageal SCC 10 years ago in China because of a lack of strong supportive care (e.g. nutritional support). Three-dimensional conformal radiation therapy (3-DCRT) could improve dose distribution, facilitating a significant increase in the target dose and reduction in the incidental dose to normal tissues.^{9,10} With the use of computed tomography

scanning, treatment fields are more accurate and matched by a significant improvement in survival. The five-year OS in definitive radiotherapy for esophageal carcinoma was 42% and 13% with or without diagnostic computed tomography scanning, respectively.¹¹ Furthermore, a lower toxicity was also observed using 3-DCRT compared with conventional two-dimensional radiotherapy.¹²

Previously, we conducted a prospective phase II study to explore the efficacy of late-course sequential boost 3-DCRT alone for esophageal SCC, and the two-year OS of 69% was attained.¹³ To our knowledge, there were limited long-term survival data on esophageal SCC using 3-DCRT or intensity-modulated radiotherapy (IMRT) alone. We decided to report these data because of the unexpected long-term outcome after the 10-year follow-up.

Methods

Patient eligibility

The study protocol was published previously.¹³ Briefly, the eligibility criteria were: (i) histologically or cytologically proven esophageal SCC of the thorax; (ii) age between 18 and 80 years; (iii) Karnofsky Performance Status of ≥ 70 ; (iv) clinical disease stages II–IVA (American Joint Committee on Cancer, 2002); and (v) unresectable or inoperable disease, or patient refusal of surgery. The local institutional review board approved this study, and all patients were required to provide informed consent at the time of enrollment.

Radiotherapy

The gross tumor volume (GTV) consisted of the primary esophageal gross tumor (GTV-P) and the metastatic nodes in the mediastinum or cardiac/cealic region (GTV-N). The planning target volume (PTV1) included a 1.2–1.5-cm margin on either side of the GTV-P or GTV-N, and a 3.0-cm margin superior and inferior to the GTV-P (along the long axis of the esophagus) to encompass any potential invasion. PTV2 encompassed GTV-P and GTV-N with a margin of 0.7 cm (Fig 1).

Computed tomography data were registered in the treatment planning system (Pinnacle; Philips Medical Systems, Hanover, MA, USA). The beam's eye view and multiplanar reconstruction facilities were used to fully encompass the PTV1 and PTV2, and minimize the dose to normal tissues. The dose was prescribed to the center of PTV2 with no correction for inhomogeneity. The treatment was delivered in two phases: 50 Gy was initially delivered to PTV1, and then a sequential boost of 16 Gy was delivered to PTV2. Both phases were completed at 2-Gy daily fractions, at five fractions per week.

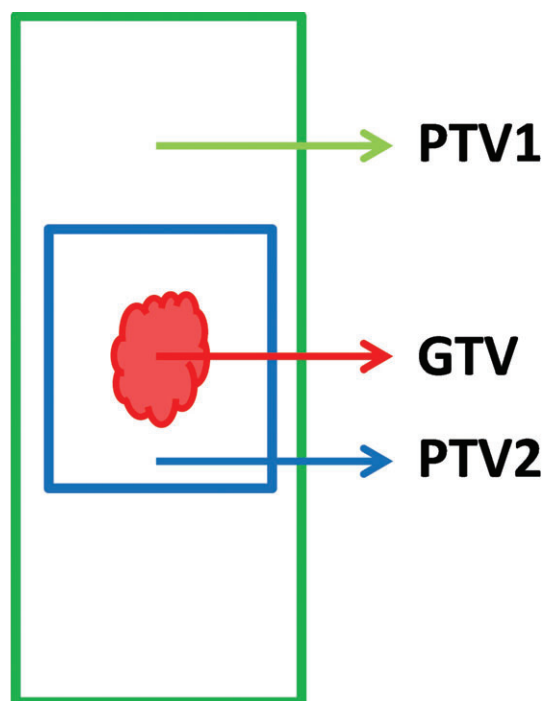


Figure 1 Definition of target volume. The planning target volume (PTV1; green frame) comprised of a 1.2–1.5-cm lateral margin around the gross tumor volume (GTV; red area), and a 3.0-cm margin superior and inferior to the GTV. PTV2 (blue frame) encompassed the GTV with a margin of 0.5–0.7 cm. The PTV1 received 50 Gy/25 fractions, whereas the PTV2 received 16 Gy/8 fractions boost, resulting in a total dose of 66 Gy.

Radiotherapy plans were typically of two types. The first type consisted of a pair of anterior and posterior portals with two oblique fields, and the other type was a three-field approach with one anterior oblique portal and two posterior oblique portals for lesions in the thorax. Optimization of the plan was based on dose-volume histogram analyses and constraints for normal structure. To fulfill the last requirement, the dose to the spinal cord had to be < 45 Gy, the mean dose to the heart had to be ≤ 40 Gy, and the proportion of the total lung volume receiving radiation of ≥ 20 Gy had to be $< 30\%$.

Statistical analysis

The statistical software package PASW statistics 20 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Descriptive statistics were calculated, and Kaplan–Meier methods were used for OS, progression-free survival (PFS), local-regional recurrence, and distant metastasis. OS was defined as the time from the first day of irradiation to that of death resulting from any cause, and PFS was defined as the time

from the first day of irradiation to that of disease progression or death resulting from any cause. Late toxicities were scored according to the RTOG/EORTC Late Radiation Morbidity Scoring Scale.¹⁴ Both univariable and multivariable Cox regression models were used to explore the potential predictors of OS, including age, sex, stage, tumor site, histology, Karnofsky Performance Status, and weight loss. Statistical significance was determined using two-sided $P < 0.05$. No corrections were made for multiplicity.

Results

Patients' characteristics

Between November 2004 and April 2007, a total of 30 patients with esophageal SCC in the thorax were enrolled in this study. The clinical characteristics have been reported previously.¹³ Briefly, 17 patients were men, and 13 patients were women. The median age was 67 years. Nine of these patients had stage II disease, 11 had stage III disease, and 10 had stage IVA disease. Seven, 13 and 10 tumors were located at the, middle, and lower thorax, respectively. The tumor sites were measured at the middle point of the tumors. The clinical characteristics of different tumor sites are shown in Table 1.

Table 1 Clinical characteristics of the 30 patients with esophageal squamous cell carcinoma

	Total (n = 30)	Upper thorax (n = 7)	Middle thorax (n = 13)	Lower thorax (n = 10)
Age (years)		64 (55–79)	65 (54–75)	68 (50–74)
Gender				
Male	17 (57%)	2 (28%)	8 (61%)	7 (70%)
Female	13 (43%)	5 (72%)	5 (39%)	3 (30%)
Stage				
IIA	9 (30%)	2 (29%)	3 (23%)	4 (40%)
IIB	4 (13%)	1 (13%)	2 (15%)	1 (10%)
III	15 (30%)	2 (29%)	8 (62%)	5 (50%)
IVA	2 (7%)	2 (29%)	0	0
Histology				
Poorly differentiated	8 (27%)	3 (43%)	2 (15%)	3 (30%)
Middle differentiated	15 (50%)	3 (43%)	7 (54%)	5 (50%)
Well differentiated	7 (23%)	1 (14%)	4 (31%)	2 (20%)
KPS				
≥90	25 (83%)	5 (71%)	11 (85%)	9 (90%)
70–90	5 (17%)	2 (28%)	2 (15%)	1 (10%)
Weight loss				
≥5%	2 (7%)	0	1 (8%)	1 (10%)
<5%	28 (93%)	7 (100%)	12 (92%)	9 (90%)

KPS, Karnofsky Performance Status

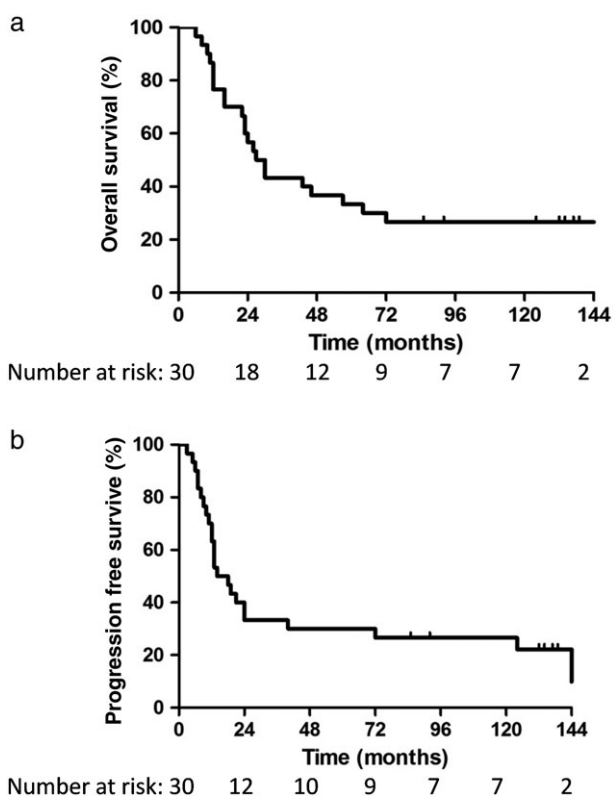


Figure 2 Kaplan–Meier curves of (a) overall survival and (b) progression-free survival for all patients.

Follow-up and survival

The median follow-up time was 30 months (range: 6–148 months) for all patients, and 132 months (range: 85–148 months) for the eight patients who were still alive until the last follow-up on 27 April 2018. The median OS was 27 months (95% confidence interval [CI] 18.9–35.0 months). The 2-, 5-, and 10-year OS rates were 56.6% (95% CI 37.4–72.1%), 33.3% (95% CI 17.5–49.9%), and 26.6% (95% CI 12.6–43.1%), respectively (Fig 2a). The median PFS was 14 months (95% CI 7.7–20.2 months), and the 2-, 5-, and 10-year PFS rates were 33.3% (95% CI 17.5–50.0%), 30.0% (95% CI 15.1–46.5%), and 26.6% (95% CI 12.6–38.7%), respectively (Fig 2b).

In long-term survival patients (over seven years and survive till last follow-up; Table 2), most tumors were in the upper thorax (5/8 patients). In the univariable and multivariable analyses, only the tumor site was associated with OS (hazard ratio [HR], 5.3, 95% CI 1.2–23.2; $P = 0.025$). The 10-year OS rates for upper, middle, and lower thorax were 71.4% (95% CI 25.8–91.9%), 15.4% (95% CI 2.4–38.7%), and 10.0% (95% CI 0.6–35.8%), respectively (Fig 3).

Table 2 Clinical characteristics of the eight long-term survivors of esophageal squamous cell carcinoma

	No. patients
Age (years)	
Median (range)	62 (55–74)
Gender	
Male	3 (37%)
Female	5 (63%)
Stage	
IIA	2 (25%)
IIB	3 (37%)
III	2 (25%)
IVA	1 (13%)
Histology	
Poorly differentiated	3 (37%)
Middle differentiated	3 (37%)
Well differentiated	2 (37%)
Tumor site	
Upper thorax	5 (63%)
Middle thorax	2 (25%)
Lower thorax	1 (12%)
KPS	
≥90	7 (88%)
70–90	1 (12%)
Weight loss	
≥5%	0
<5%	8 (100%)

KPS, Karnofsky Performance Status

Pattern of failure

Most patients died of tumor progression, except for one patient who died of stroke, and two patients who died of lung infections. A total of 14 patients suffered local-regional recurrence, four patients suffered distant metastasis, and three suffered local-regional and distant metastasis. The 2-, 5-, and 10-year local-regional recurrence rates were 50.3% (95% CI 30.7–67.0%), 61.7% (95% CI 45.1–74.6%),

and 68.1% (95% CI 52.3–79.6%), respectively. The 2-, 5-, and 10-year distant metastasis rates were 34.6% (95% CI 12.7–58.0%), 34.6% (95% CI 12.7–58.0%), and 34.6% (95% CI 12.7–58.0%), respectively. Among the long-term survivors, one patient had recurrence of the supraclavicular lymph lode and another had bone metastasis, at 10 and 12 years after radiation, respectively.

Six patients received salvage treatment due to local recurrent or distance metastasis; four of these patients received two types of salvage treatments. Chemotherapy was not administered according to the scheme. However, three patients received chemotherapy consisting of 5-fluorouracil and cisplatin to treat local relapse or distant metastases after radiotherapy. Three patients received rescue surgery for recurrence after completing radiotherapy (at 13 months in one case and 12 months in the other two cases). Two patients underwent stent placement as a palliative treatment, and two patients received re-radiation for local recurrence.

Late toxicity

Grade 2 (*n* = 1) and grade 3 (*n* = 1) symptomatic pulmonary fibrosis were observed. Three patients developed mild esophageal stricture, two of whom required dilatation, one year after radiotherapy. No heart or other late toxicity was observed. Furthermore, the long-term survivors lived without severe late toxicity.

Discussion

Concurrent chemoradiotherapy is the standard treatment for locally advanced esophageal cancer.^{5–7} However, concurrent chemotherapy significantly increased acute toxicity, especially esophagitis, and just 68% of patients could complete chemotherapy as planned.⁵ A poor prognosis was previously found for esophageal cancer treated with two-dimensional conventionally fractionated radiation alone (five-year OS of 0–9%).^{5,15} Here, we reported a 10-year OS of 26.7% for 3-DCRT alone. In another prospective phase II trial from our group, 53 patients received late-course accelerated hyperfractionated (LCAF) 3-DCRT at a dose of 68.4 Gy in 41 fractions over 44 days without chemotherapy.⁸ The OS at one, two, and three years were 77%, 56%, and 41%, respectively. LCAF two-dimensional radiotherapy has also been found to be effective for esophageal SCC. Zhao *et al.* reported that the one-, three-, and five-year OS were 73%, 34%, and 26%, respectively, in 201 esophageal SCC patients who received LCAF without chemotherapy.¹⁶ These authors then conducted a phase III trial to compare LCAF radiotherapy with and without concurrent chemotherapy.¹⁷ No significant differences were found between these two groups, and the five-year OS rates were 40% and

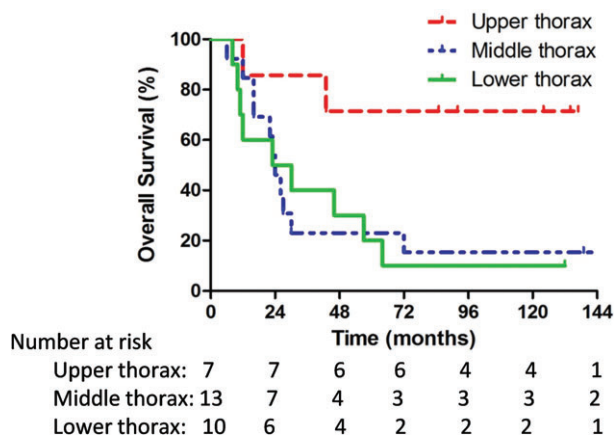


Figure 3 Kaplan–Meier curves of overall survival for the different tumor sites. Log-rank (Mantel–Cox) test: *P* = 0.048.

28%, respectively ($P = 0.31$). The long-term follow-up of these patients supports the previous conclusion. The 10-year OS rates were 19% and 23%, respectively.¹⁸ An acceptable OS with radiotherapy alone has also been reported in other retrospective studies.^{19–21} All these data suggest a non-trivial role for radiotherapy alone, especially 3-DCRT, for esophageal SCC.

The target volume of this trial was smaller than that of the RTOG 85-01 and RTOG 94-05 study.^{5,7} Involved-field irradiation was used in this trial, as shown in Figure 1. In the RTOG 85-01 study, the irradiation field was extended from the supraclavicular region to the gastroesophageal junction; however, the supraclavicular nodes were omitted in patients with tumors in the lower third of the esophagus. The incident of out-field recurrence of involved-field irradiation was low. Just three of 39 and two of 63 out-field recurrences were observed in the studies by Zhao and Hidomi.^{8,22} In a retrospective study, there were differences in the three-year local control (44.8% vs. 55.5%; $P = 0.039$), distant control (53.8% vs. 69.9%; $P = 0.021$), and OS (34.8% vs. 51.6%; $P = 0.087$) between elective nodal irradiation versus involved-field irradiation, respectively.²³ A significantly low risk of high-grade late toxicities was also observed (8% vs. 16%; $P = 0.047$). Decreasing the target volume could reduce the mean body dose, which could contribute to a better outcome.²⁴

Although 50.4 Gy remains the standard dose of chemoradiation for esophageal cancer,^{7,25,26} authors of some large popular based retrospective studies showed the survival benefit of having a dose ≥ 60 Gy.²⁷ The primary tumor position is the most frequent recurrence position after radiotherapy,^{8,22,28} suggesting an insufficient dose to the primary tumor. A sequential boost of 16 Gy was added to the gross tumors in this trial, and the gross tumors received 66 Gy in total, which was considered to be a safe method of boost dose. Low acute and late toxicity were observed in this trial.¹³ Some other boost dose methods have been explored, including brachytherapy²⁹ and simultaneous integrated boost IMRT (SIB-IMRT).^{27,30–34} Severe toxicities were observed in the former method, including 24% of life-threatening toxicity and 10% of treatment-related death.²⁹ SIB-IMRT was promising for improving survival, and a two-year OS of 72.7% was reported in a phase II study.³² A higher frequency of acute esophagitis was observed in the SIB-IMRT study than for IMRT, used in this study (Table S1). This might partly be because no chemotherapy was used in this study. In addition, the fraction dose of 2.2–2.5 Gy used in SIB was higher than that used in this study (2 Gy). Although the benefit of dose escalation has not yet been evaluated, a high dose (66 Gy) to the gross tumor, as used in this trial, is suggested in the absence of chemotherapy.

We showed that the tumor site was the only predictor for esophageal SCC treated by 3-DCRT alone. Tumors located in the upper thorax had better prognosis compared with other locations. The 10-year OS for upper, middle, and lower thorax were 71.4%, 15.4%, and 10.0%, respectively. In long-term survivors, 75% of patients had node-positive locally advanced cancers (Table 2), suggesting that the better prognosis was not due to an earlier stage. It is unknown why the upper esophageal cancer had a higher survival benefit. One reason might be the lower exposure of the lungs and heart to radiation. This might have resulted from false positives due to sample size.

For supportive medicine, concurrent chemoradiation is currently widely administered for esophageal cancer in China. Although the OS was promising, the local-regional control and metastasis were disappointing. The 10-year local-regional recurrent and metastasis rates were as high as 68.1% and 34.6%, respectively. High-dose 3-DCRT combined with concurrent chemotherapy or immunotherapy to the gross tumors, especially more invasive esophageal SCC, is worth exploring in future studies.

In conclusion, the late-course sequential boost 3-DCRT to esophageal SCC is safe and feasible. The long-term outcome of the late-course sequential boost 3-DCRT alone for esophageal SCC is encouraging. The role of radiotherapy alone for esophageal SCC is underestimated in the development of technology.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Toxicity between simultaneous integrated boost intensity-modulated radiotherapy and late-course sequential boost three-dimensional conformal radiotherapy.