RESEARCH ARTICLE

Moderately Hypofractionated Conformal Radiation Treatment of Thoracic Esophageal Carcinoma

Jin-Bo Ma[1,2], Lin Wei[2]*, Er-Cheng Chen[1]*, Guang Qin[2], Yi-Peng Song[1], Xiang-Ming Chen[2], Chuan-Guo Hao[2]

Abstract

Aims: To prospectively assess the efficacy and safety of moderately hypofractionated conformal radiotherapy in patients with thoracic esophageal cancer. Methods and Materials: From Sept. 2002 to Oct. 2005, 150 eligible patients with T2-4N0-1M0 stage thoracic esophageal squamous cell cancers were enrolled to receive either conventional fractionated radiation (CFR) or moderately hypofractionated radiation (MHR) with a three-dimensional conformal radiation technique. Of the total, 74 received moderately hypofractionated radiation with total dose of 54-60Gy/18-20fractions for 3.5-4 weeks in the MHR arm, and 76 received conventional radiation with total dose of 60Gy/30 fractions for 6 weeks in the CFR arm. Concurrent chemotherapy comprised of paclitaxel and cisplatin. Safety was evaluated, and local control and overall survival rates were calculated. Results: Statistically significant differences between the CFR versus MHR arms were observed in local/regional failure rate (47.3% v 27.0%, P=0.034) and the percentage of patients with persistent local disease (26.3% v 10.8%, P=0.012). But 3 and 5-year overall survival rates (43.2%, 38.8% v 38.2%, 28.0%, respectively) were not different between the two arms (P=0.268). There were no significant differences in the incidences of grade 3 or higher acute toxicities (66.3% v 50.0%) and late complications rates (27.0% v 22.4%) between the MHR and CFR arms. Conclusions: Moderately hypofractionated, three-dimensional radiation treatment could improve the local control rate of esophageal cancer and potentially increase patients' survival.

Keywords: Chemoradiation - esophageal cancer - hypofractionated radiation

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Introduction

Radiation or chemoradiation therapy was one of optional treatments for esophageal cancer with the average 5-year overall survival rate of 25% (Cooper et al., 1999). Local and/or regional failure is the most important treatment failure associated with this therapy. Tumor regional persistence is the major cause of local failure for the standard chemoradiation therapy of esophageal cancer. In RTOG9405 study the rate of local/regional failure for esophageal cancer was 50%-55%, with more than 30% local failure attributed to regional tumor persistence after radiation (Minsky et al., 2002). But distant failure was only from 9% to 16%. RTOG9207 trial concluded with the same results (Gaspar et al., 2000). These findings indicated that conventional fraction scheme produced radiobiologically less tumoricidal effects for radio-resistant esophageal cancer (Halperin et al., 2008). Recent literature reported that radiation increased the expression of cancer stem cells markers for radiation resistance (Bao et al., 2006; Hermann et al., 2007; Nguyen et al., 2011), which could lead to the local failure. To increase local control after radiation, fraction dose or total dose should be further increased. But the results of RTOG9405 study did not support the dose escalation with conventional fraction to improve survival. But hypofractionated external radiation scheme of esophageal cancer would require be further proved in the trial.

Currently most hypofractionated radiations for esophageal carcinoma are performed as brachytherapy (Sykes et al., 1998; Hama et al., 2002; Song et al., 2011), without demonstrating clear benefit as an adjuvant treatment. Few studies about hypofractionated external beam radiation were reported. Sykes AJ reported the result of hypofractionated radiation for the treatment of esophageal carcinoma (Sykes et al., 1998), in which 5-year survival rate was 42% with diagnostic CT scanning, but only 13% without diagnostic CT scanning. Our previous phase I/II study of fraction dose escalation indicated that hypofractionated radiation improved the local control of esophageal carcinoma (Song et al., 2011). Subsequently, we conducted this study to investigate the results of hypofractionated conformal radiation for the treatment of thoracic esophageal carcinoma.

*[1]Department of Radiation Oncology, Yantai Yuhuangding Hospital, School of Medicine, Qingdao University, Yantai, [2]Center of Radiation Oncology, The Central Hospital of Tai An, Taian, China [&]Equal contributors *For correspondence: chenercheng@163.com; wlin788@163.com*

Materials and Methods

Patient population

From September 2002 to December 2005, 150 patients with thoracic esophageal cancer nonrandomly received either conventional or hypofractionated radiation according to patients' preferences at Center of Radiation Oncology in the Central Hospital of TaiAn (TaiAn, China). Of them, 110 were men 40 were women, with a median age of 64 years (Range 45-74). Seventy four patients completed moderately hypofractionated conformal radiation treatment with a total dose of 54-60Gy/18-20fractions/3.5-4 weeks and there was no correction for lung tissue heterogeneity. A total of 76 patients received conventional fraction scheme with a total dose of 60Gy/30fractions/6weeks. Twenty six patients were at stage T2, 79 at stage T3, and 45 at stage T4 without recurrent diseases at the time of treatment initiation. According to the American Joint Committee on Cancer (AJCC) TNM 2002 staging system (Greene et al., 2006), 135 patients were at stage N0 and 15 at stage N1. The median tumor length was 7 cm (Rang 3.5-8.5 cm). Patients' characteristics for different fractionated dose were summarized in Table 1. Karnofsky performance status was ≥ 70 for all patients. Pretreatment examinations included medical history and physical examination, complete blood cell count, electrocardiogram, chest radiograph, esophageal barium-swallow imaging, esophagoscopy, chest computed tomography (CT) scan, bone scan, ultrasonic examination for abdomen, including liver, kidney, spleen, and retroperitoneal lymph nodes. The research has complied with all relevant national regulations and institutional policies and has been approved by the both hospitals' institutional review boards. The procedures followed were in accordance with the Helsinki Declaration.

Table 1. Patients Characteristics

	Hypofractionated Arm (n=74)	Conventional Arm (n=76)
Total dose	54-60Gy	60Gy
Age(years)		
<65	23(31.1%)	26(34.2%)
≥65	51(68.9%)	50(65.8%)
Median	64	63
Range	45-74	41-70
Gender		
Male	51(68.9%)	59(77.6%)
Female	23(31.1%)	17(22.4%)
T stage		
T2	11(14.9%)	15(19.7%)
T3	40(54.0%)	39(51.4%)
T4	23(31.1%)	22(28.9%)
N stage		
N0	67(90.5%)	68(89.5%)
N1	7(9.5%)	8(10.5%)
Site		
Upper-thoracic	21(28.4%)	20(26.3%)
Middle-thoracic	49(66.2%)	54(71.1%)
Lower-thoracic	4(5.4%)	2(2.6%)
Length (cm)		
≤5	22(29.7%)	18(23.7%)
>5	52(70.3%)	58(76.3%)
Median	6.5	7
Range	3.5-8	4-8.5

Treatment

Patients did not receive any cancer treatment prior to radiation therapy. During the study, all patients also received concurrent chemotherapy. During the period of radiation therapy, patients received 60 mg/m^2 of paclitaxel (Haikou Municipal Pharmaceutical Co., Ltd, China) by intravenous infusion once a week. Then patients received 2 cycles of chemotherapy after the completion of radiation therapy. The chemotherapy consisted of 120 mg/m^2 of paclitaxel d1 plus 30 mg/m2 of cisplatin (Qilu Pharmaceutical Co., Ltd, China) on d1-3 by rapid intravenous infusion.

Three-dimensional conformal radiation technique was applied to the involved field in the study (Zhao et al., 2010; Kawaguchi et al., 2011). CT (Sensation 16, Siemens, German) images were obtained from the thyroid notch level to the lower border of the second lumbar vertebra. The gross tumor volume (GTV) was delineated, including all visible tumors based on the imaging. The planning target volume (PTV) was also delineated with consideration of organ motion and uncertainty of setup. The images were then transferred to the 3-D planning system (Versus R V2.20, Topslane, China). A dose of 54-60 Gy with fraction dose 3Gy was delivered according to PTV. Dose–volume histograms (DVHs) and biological indices for target volume and normal organ were evaluated and compared. The maximum spinal cord dose was ≤40 Gy. The volumetric percentage of the whole lungs which received a radiation dose of ≤20 Gy, was ≤ 30% to decrease the risk of severe complications. Worsening of lung function was expected to be higher even for 3D-CRT. Treatments were designed using computerized radiation dosimetry, and delivered by 6-MV X-rays from a linear accelerator (Primus M; Siemens, German).

During the treatment, patients were monitored for signs or symptoms of hematologic, pulmonary, or gastrointestinal toxicity every week. When Grade ≥ 3 toxicities were observed, supportive therapy was provided and appropriate adjustments to the radiotherapy were made, including withholding the treatment.

Follow-up evaluation and statistical analysis

The monitoring of Toxicity was performed according to the Radiation Therapy Oncology Group criteria and the National Cancer Institute Common Terminology Criteria and Adverse Events (CTCAE) version 3.0 (Trotti et al., 2003). All patients underwent esophagoscopy to determine whether there was a persistent local disease in esophagus at 2 months intervals after chemoradiatiotherapy. The patients were also evaluated by physical examination, complete blood cell count, esophageal barium-swallow imaging, and ultrasonic examination for abdomen or thoracic CT scan at 2- or 3-month intervals after chemoradiotherapy. Treatment failure was analyzed for local, regional, and distant metastasis. Local recurrence was defined as any recurrence of the primary tumor, including persistent disease after initial treatment. Recurrent or newly developed mediastinal or

Table 2. Acute Toxicities and Late Complications for All Patients

Grade	Acute Toxicities				late complications			
	Hypofractionated (n=74)		Conventional (n=76)		Hypofractionated (n=74)		Conventional (n=76)	
	No.	%	No.	%	No.	%	No.	%
1	6	8.1	9	11.8	12	16.2	9	11.8
2	17	23	18	23.7	19	25.7	14	18.4
3	31	41.9	27	35.5	10	13.5	11	14.5
4	15	20.3	10	13.2	7	9.5	5	6.6
5	3	4.1	1	1.3	3	4.1	1	1.3

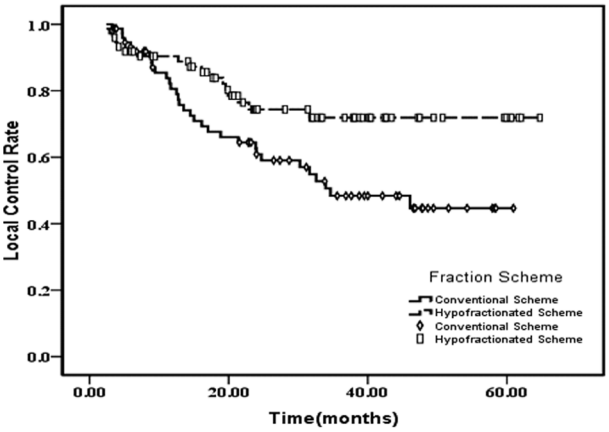

Figure 1. Local Control Rates of Esophageal Cancer with Hypofractioned Scheme Versus Conventional Fraction Scheme (P=0.020)

supraclavicular lymphadenopathy was defined as regional recurrence, and distant metastasis was defined as any recurrence of systemic organs. The survival time was counted from the start of radiotherapy to the date of death or the last follow-up. Statistical analyses were conducted using SPSS version 13.0. Overall survivals and local control were calculated by the Kaplan-Meier method. Cox proportional hazard model was used to analyze prognostic factors.

Results

Total follow-up time ranged from 6 months to 60months. The median follow-up period for survivors was 38 months.

Treatment-related toxicities and cause of death

Treatment-related toxicities in the trial were summarized in Table 2. There were no statistically significant differences on the incidence rates of grade 3 or higher acute toxicities (66.3% v 50.0%, respectively) and late complications (27.0% v 22.4%, respectively) between MHR and CFR arms (P>0.05). The peak time for the occurrence of acute toxicities was the first week during radiation in hypofractionated arm. A total of 6 treatment-related deaths were identified, due to esophageal fistulas, pneumonia, cardiac or hematologic toxicities, in the MHR arm, compared to only 2 treatment-related deaths in the CFR arm. The incidence of Esophageal Grade 3 or higher late complications (18.9% v 21.1%, respectively), including stenosis, fistula or hemorrhage, was also similar between the MHR and CFR arms.

Table 3. Patterns of Treatment Failure

	Hypofractionated (n=74)		Conventional (n=76)	
	No.	%	No.	%
Alive/no failure	32	43.2	24	31.6
Total failure	34	45.9	47	61.8
Persistent local disease	8	10.8	20	26.3
Local failure	7	9.5	8	10.5
Regional failure	3	3.9	3	3.9
Distant failure	14	18.9	11	14.5
Local/regional/distant failure	4	5.4	7	9.2
Treatment-related death	3	3.9	1	1.3
Cancer death	34	45.9	45	59.2
Dead of medicine disease/ or not specified	3	3.9	2	2.7

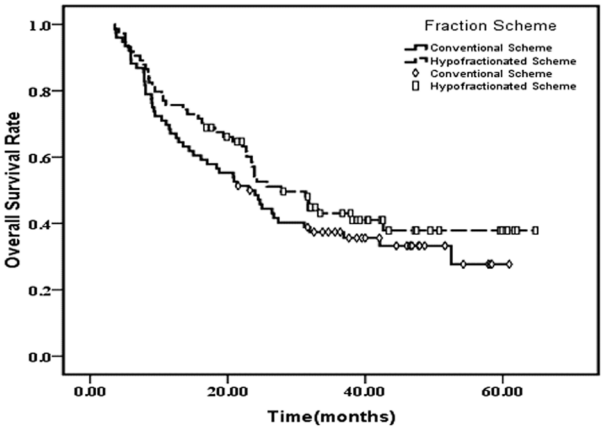

Figure 2. Overall Survival Rates of Esophageal Cancer with Hypofractioned Scheme Versus Conventional Fraction Scheme (P=0.268)

Local control and overall survival rate

Although 3- and 5-year survival rates (43.2% and 38.8%, 38.2% and 28.0%, respectively) were not significantly different between the hypofractionated and conventional schemes (P=0.268), 3- and 5-year local control rates were different (81.4% and 50.0% versus 71.8% and 44.1%, respectively) (P=0.02). Also, the median survival time was 23.0 months (95%CI 16.6, 29.5) and 27.8 months (95%CI 20.7, 28.2) for the conventional and hypofractionated scheme respectively.

Failure patterns

The patterns of treatment failures are summarized in Table 3. Statistically significant difference was observed in rates of local/regional failure (47.3% v 27.0%, P=0.034) and persistent local disease (26.3% v 10.8%, P=0.012) between the CFR and MHR arms. But there was no statistical difference in the rate of local/regional failure (23.6% v 18.8%) between two arms (P=0.368), except for persistent local disease. The rate of distant failure was also similar between two arms (23.7% v 24.3%, respectively) (P=0.485).

Discussion

Since esophagus is a hollow tubular organ, high fraction dose could cause serious adverse effects, such as esophageal stenosis, hemorrhage, perforation, etc (Hama, et al., 2002, Halperin, et al., 2008). Our previous

phase I/II study of fraction dose escalation indicated that daily dose of ≤5 Gy was appropriate in hypofractionated radiation for the treatment of esophageal carcinoma (Song, et al., 2011). In addition, literature from hypofractionated brachytherapy did not support fraction dose higher than 5 Gy (Hama, et al., 2002; Kassam et al., 2008; Song, et al., 2011). Therefore, moderately hypofractionated radiation was used in this study.

In this study 5-year local control rate (81%) was significantly increased in the hypofractionated fraction scheme arm when compared to conventional fraction scheme arm, likely owing to the hypofractionated radiobiological response. The gastroscope-guided cytopathological examination also showed low rate of regional persistence for the tumor (15%) in esophagus after radiation, which was lower than 31.6% in conventional scheme arm and ≥30% reported in the RTOG94-05 trial (Minsky et al., 2002). "Vaccine response" from immunization should be one of causes for better local control since the exposure of tumor antigen from many tumor cells died during hypofractionated radiation (Lee et al., 2009). Given the improvement in local control, there was a clear trend in favor of hypofractionated radiation over conventional radiation on overall survival rate (38.2% v 28%). Harney J et al. reported that 1-year disease-free rate was 50% and 3.5-year was 35% for hypofractionated radiation-treated esophageal cancer (Harney et al., 2003). A trial by Vuong T et al. indicated that the 2-year local recurrence rate was 25% and the 5-year survival rate was 28% (Vuong et al., 2005). These results indicated that for the treatment of esophageal carcinoma hypofractionated radiation offered a clear advantage over conventional radiation, especially in local control.

For esophageal carcinoma, one of major toxicities associated with radiation or chemoradiation therapy was radiation pneumonia. With the development of 3DCR/IMRT and involved-field (Zhao et al., 2010; Kawaguchi et al., 2011) technique, the control of radiated-related pulmonary injury became possible for the radiation treatment of esophageal cancer. In this trial moderately hypofractionated conformal radiation did not increase the rate of severe (≥ grade 3) radiation pneumonia (3.7%), which was 5%-10% in the literature (Harney et al., 2003; Vuong et al., 2005; Vogelius et al., 2010)

RTOG trials showed that severe (grade ≥3) acute esophageal toxicities occurred in 25%-60% of esophageal cancer patients received chemoradiation therapy (Cooper et al., 1999; Gaspar et al., 2000; Minsky et al., 2002). In the trial, the rate of severe acute esophageal toxicities was 41.1% (31/74) in the MHR arm. Late stenosis and esophageal fistulas were other safety concerns for hypofractionated radiation since they could lead to mortality. Long-term results from RTOG study indicated that grade ≥3 late esophageal complications occurred in 23% to 29% of patients (Cooper et al., 1999; Minsky et al., 2002). In this trial the rate of late esophageal complications in MHR arm, including stenosis and fistulas, was 18.9%, which was slightly lower comparing to 21.1% in CFR arm. Possible factors associated with esophageal late complications include T stage of the tumor, the circumference of the tumor, and esophageal wall thickness of the tumor region, as reported in the literatures (Khurana et al., 2007; Atsumi et al., 2010). Other trials reported similar results of hypofractionated radiotherapy for esophageal carcinoma (Harney et al., 2003; Brunner et al., 2008; Kassam et al., 2008; Seung et al., 2008).

In conclusion, Three-dimensional moderately hypofractionated radiation and the use of involved field could decrease the risk of persistent local disease with a clear tendency toward additional survival benefit, compared to conventional radiation, for the treatment of esophageal cancer

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The author(s) declare that they have no competing interests.

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