RESEARCH COMMUNICATION

Efficacy Analysis of Simplified Intensity-modulated Radiotherapy with High or Conventional Dose and Concurrent Chemotherapy for Patients with Neck and Upper Thoracic Esophageal Carcinoma

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Abstract

For patients with neck and upper thoracic esophageal carcinoma, it is difficult to control lymph node metastases with conventional dose therapy. In this study, we assessed the feasibility of simplified intensity-modulated radiotherapy (sIMRT) and concurrent chemotherapy for 44 patients and boosted high-dose to metastatic lymph nodes.Three radiation treatment volumes were defined: PGTVnd, with which 68.1Gy was delivered in high dose group (hsIMRT group), and 60Gy in the conventional dose group (csIMRT group); PTV1, featuring 63.9Gy in the hsIMRT group and 60Gy in the csIMRT group; PTV2, with 54Gy given to both groups. The sIMRT plan included 5 equi-angular coplanar beams. All patients received the cisplatin and 5-FU regimen concurrently with radiotherapy. The treatment was completed within six weeks and one case with grade three acute bronchitis was observed in hsIMRT group. For esophageal lesions, 80% complete response (CR) and 20% partial response (PR) rates were found in the hsIMRT group, and 79.2% CR, with 20.8% PR, in the csIMRT group; for lymph node lesions, 75% CR and 25% PR rates were observed in the hsIMRT group, with 45.8% and 37.5% respectively in the csIMRT group (P <0.05). The differences in 1-, 2- and 3-year relapse-free survival rates were all statistically significant (P <0.05). The major toxicity observed in both groups was Grade I~II leucopenia. sIMRT can generate a desirable dose distribution in treatment of neck and upper thoracic esophageal carcinoma with a better short-term efficacy. Boosted high dosing to metastatic lymph nodes can increase the relapse-free survival rate.

Keywords: Esophageal carcinoma - simplified intensity - modulated radiotherapy - chemotherapy - prognosis

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Introduction

Neck or upper thoracic esophageal carcinoma with lymph node metastasis is a common clinical disease with poor prognosis (Kawahara et al., 1998; Kurokawa et al., 2003; Xiao et al. 2003; Xiao et al., 2005; Tachimori et al., 2011). Due to hypoxia, metastatic lymph node is difficult to control by radiotherapy with the conventional dose, especially those large metastatic lymph nodes (Watarai et al., 1992). Meanwhile, as the decline of the life quality can be easily caused by surgical treatment, surgery is hardly accepted by the sufferers (Denham et al., 1996). Even worse, the dose to the tumor and surrounding region (target volume) is heterogeneously delivered due to anatomic changes between neck and upper thorax dimensions, especially with conventional or three-dimensional conformal radiotherapy (Tai et al., 1998; 2000).

Intensity modulation radiation therapy (IMRT) is a technique using a multi leaf collimator (MLC) to form multiple segments for step-and-shoot. Though IMRT can solve the problem of target dose distribution, it results in the prolongation of time of therapy due to the large number of segments and a small area of each segment, which, consequently, is apt to cause great dose errors via the locomotion of bodily organs. Apart from that, for each patient undergoing IMRT, correct dose should be verified, which inevitably takes up a lot of manpower and material resources.

To avoid the above-mentioned limitations of different treatment methods, a technique, named simplified intensity modulated radiation therapy (sIMRT) (Geng et al., 2006). This has been defined by the Tumour Hospital of Chinese Academy of Medical Sciences, was adopted in treatment of neck or upper thoracic esophageal carcinoma with lymph node metastasis in this study. Among total 44 patients, 20 were given sIMRT using the simultaneous integrate the boost (SIB-sIMRT) techniques to higher dose while the others were given sIMRT using the conventional dose. Here, the short-term curative effects, radiation reactions, and 1-, 2- and 3-year survival rates between

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two groups were compared and reported.

Materials and Methods

Patients

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Huai'an First Hospital. Written informed consent was obtained from all participants. From January 2007 to December 2007, 44 patients suffering from neck or upper thoracic esophageal carcinoma with lymph node metastasis received sIMRT in Huai'an First Hospital, China. Among them, 29 were males and 15 females with the median age of 57 (range, 46~68). All the cases were squamous cell carcinoma detected under esophagoscope. Performance statue score lower than or equal to 1 (according to ECOG). The diameter of lymph node < 2 cm was found in 16 cases and that ≥ 2 cm in 28 cases with the largest 5.5 cm × 4.0 cm. Short diameter > 1.0 cm was used as the threshold of metastatic lymph node in CT slices and endoscopic ultrasound (but diameter > 0.5 cm as the base when delineating lymph node target site). All the patients had no distant metastasis and a history of radiochemotherapy or contraindications of radiochemotherapy. The patients were randomly divided into hsIMRT group (sIMRT with high dose, 20 cases) and csIMRT group (sIMRT with conventional dose, 24 cases) by sealed envelope method.

Radiotherapy

Radiotherapy was performed using Siemens ONCOR accelerator. The patient was supine on the treatment frame with the thermoplastic mask of head, neck and shoulders for fixation, and then consecutively underwent enhanced CT scanning under normal respiration with the scan slice thick 5 mm. After capture of localization image, the outlines of lesions and organs at risk (normal organs such as lung and spine marrow need to be avoided) were delineated in accordance with the following criteria: 1. GTV (gross tumor volume), consisting of primary tumor (designated GTVnx) and lymph node metastasis (designated GTVnd): the upper and lower bounds were determined based on the results of esophagograms and CT, and lymph node > 0.5 cm was included in GTV; 2. CTV1 (clinical tumor volume) and CTV2 (after the delineation of GTV): CTV1 was defined as beyond GTVnx 3~3.5 cm vertically, 0.5 cm laterally and anteriorly, and 0.3~0.5 cm posteriorly while CTV2 encompassed the supraclavicular lymph node area below cricothyroid membranes as well as 2, 3, 4, 5, 7 lymph node areas at the chest. The different lymph node areas were determined according to related literature (Korst et al., 1998); 3. PTV (plan tumor volume): PGTVnd was beyond GTVnd 0.5 cm. considering the small influence of respiratory movement on neck and upper thoracic esophageal carcinoma and stable immobilization of the thermoplastic mask, PTV1 was defined as CTV1 plus a margin of 0.5 cm, and PTV2 as CTV2 plus a margin of 0.5 cm. The sIMRT plan of five equiangular coplanar beams was designed by CMSXIO4.33 system: 0°, 72°, 144°, 216° and 288°. sIMRT was defined as a intensity modulated radiotherapeutic technique with the average number of segments per beam ≤ 5, the segments area ≥ 10 cm^2 and the machine monitor for each segment ≥ 10 MU. All the patients were randomly divided into hsIMRT group (20 cases) and csIMRT group (24 cases). PGTVnd in hsIMRT group was given 68.1Gy (2.27Gy×30 fractions) and that in csIMRT group was given 60Gy (2.0Gy×30 fractions). As PTV1 was the target volume of primary lesion, 63.9Gy (2.13Gy×30 fractions) was delivered in hsIMRT group and 60Gy (2.0Gy×30 fractions) in csIMRT group. PTV2 was the prophylacticly irradiated volume, to which 54Gy (1.8Gy×30) was given in both groups. Bilateral lungs: V20 ≤ 25% and V30 ≤ 20%. Spinal marrow: ≤ 45Gy (Table 1).

Table 1 The Radiation Doses to Target Regions and Requirements for Organs at Risk

target volumes	hsIMRT group dose (Gy)	csIMRT group dose (Gy)	V20(%)	V30(%)
PGTVnd	68.1	60		
PTV1	63.9	60		
PTV2	54	54		
spinal marrow	≤45	≤45		
left lung			<25	<20
right lung			<25	<20

And the optimal weights of constrained conditions were sequenced as follows: PGTVnd > PTV1 > PTV2 > spinal marrow > whole lungs. After all these requirements were satisfied, shifts were carried out under the analog model. As the segments area and the number of monitor units of each segment were close to those for 3D-CRT, dose verification for sIMRT was only done during try-out period. After first treatment using electron portal imaging device (EPID) for location re-identification, formal treatment started (Table 1).

Chemotherapy

All patients received two courses of the treatment with cisplatin (DDP) and 5-FU concurrently with radiotherapy on Day 1-5 and 29-33: 75 mg/m^2 DDP iv drip on Day 1, and 5-FU 3.0g/m^2 for 96 h. Then, two courses of the same treatment were carried out on Day 28 after the completion of radiotherapy.

Outcome measures

Acute radiation reactions were evaluated according to the criteria by PTOG (radiation therapy oncology group, USA). Chemotherapeutic toxicity according to CTCAE (Common Terminology Criteria for Adverse Events v3.0) (Trotti et al., 2003), effects after radiotherapy for esophageal carcinoma according to the criteria specified in literature (Wan et al., l989). Lymph nodes were evaluated as solid tumor according to the criteria of WHO (Palmer, 1982). On account of the possible false positive of lymph nodes ≤1.0 cm and evaluation difficulties, evaluations of effects were only confined to those nodes >1.0 cm in this study. The primary endpoint was relapse-free survival rate, the secondary endpoint were overall survival rate and short-term effect.

Statistical analysis

Dose-volume histogram (DVH) was used to evaluate

Table 2 The Radiation Doses to Target Regions and Organs at Risk of 20 Cases in hsIMRT Group

target volumes	maximum dose (Gy)	minimum dose (Gy)	mean dose (Gy)	V20(%)	V30(%)
PGTVnd	72.35±1.35*	64.2±1.68	68.40±0.80		
PTV1	68.10±1.45	60.80±1.39	64.50±0.74		
PTV2	72.35±1.35*	44.60±1.75	56.55±0.72		
spinal marrow	42.75±1.46	14.60±1.78	18.35±1.25		
left lung				23.95±3.75	11.90±2.78
right lung				23.50±2.50	10.65±1.48

*As PGTVnd was included in PTV2 by CMS XIO 4.33 TPS software in our unit, the maximum doses to PGTVnd and PTV2 were the same

Table 3 The Radiation Doses to Target Regions and Organs at Risk of 20 Cases in hsIMRT Group

target volumes	maximum dose (Gy)	minimum dose (Gy)	mean dose (Gy)	V20(%)	V30(%)
PGTVnd	64.55±1.96*	57.86±1.75	60.45±1.15		
PTV1	65.20±1.48	58.10±1.73	60.94±0.55		
PTV2	64.55±1.96*	43.56±1.67	55.70±0.80		
spinal marrow	40.45±1.25	12.60±1.55	15.35±1.45		
left lung				21.60±3.15	10.75±2.75
right lung				19.50±2.15	8.70±1.15

*As PGTVnd was included in PTV2 by CMS XIO 4.33 TPS software in our unit, the maximum doses to PGTVnd and PTV2 were the same

the satisfaction of clinical dose requirements of treatment plans, and the statistical indexes included: the maximum, minimum, and mean radiation dose to PGTVnd, PTV1 and PTV2, respectively; the maximum and mean dose to organs at risk, and V20, V30 of lungs. Survival time was counted from the time of confirmed diagnosis to the death time. Relapse-free survival was defined as the period between the first date of diagnosis and the day when dis¬ease relapse was detected. The enumeration data were analyzed using χ^2 and computed using SPSS13.0 statistical software. Kaplan-Meier method and Logrank test were used for survival analysis.

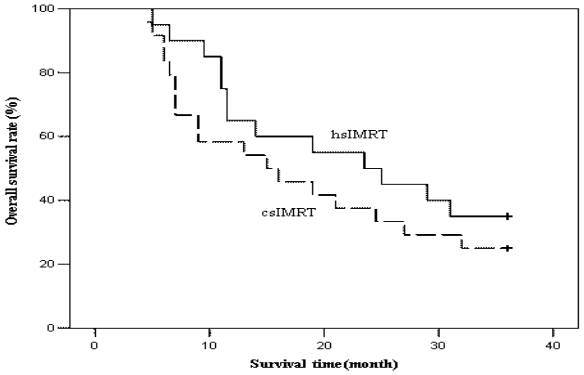

Figure 1. The Overall Survival Curves of hsIMRT Group and csIMRT Group. The overall survival rate of 1-, 2- and 3-year was 65%, 50% and 35% in hsIMRT group, and 58.3%, 37.5 and 25% in csIMRT group, respectively, displaying no statistically significant differences (χ^2=1.024, P> 0.05)

Results

Dose distribution in target regions and organs at risk The mean values of radiation dose to target regions and organs at risk in hsIMRT group were showed in Table 2. It proved that the hsIMRT plan could basically meet clinical requirements, with the mean dose of 68.40Gy to PGTVnd, 64.50Gy to PTV1 and 56.55Gy to PTV2. The target dose distribution in csIMRT group well satisfied clinical requirements, and the radiation dose to organs at risk was in a tolerable range, clinically (Table 3).

Duration time of treatment

During treatment, the dose rate of 200 MU/min was employed.The hsIMRT, which contained average 25 ±5.5 segments, had 360±22 as its total MU value. the csIMRT, which contained average 25±4.5 segments, had 345±18 as its total MU value. The execution times for these treatments were 8.2±0.7 min for hsIMRT, 7.7±1.1 min for csIMRT, the treatment time for hsIMRT was slightly longer than csIMRT.

Acute therapeutic reactions

Acute radiotherapeutic reactions among all patients mainly took the forms of radiation-induce bronchitis and esophagitis. The clinical symptom of radiation-induced bronchitis was cough, and 8 cases (18.2%) were found with Grades I and II among all patients and 1 case with Grade III in hsIMRT group. The main symptom of radiation-induced esophagitis (36.4%) with Grade I~II was pain when taking food (pharyngalgia in some patients). Haematology toxicity was mainly manifested by Grade I~II leucopenia, which didn't cause treatment interruption after leukopoietic treatment. And no advanced-stage radiation damage was found.

Short-term effect

For esophageal lesion, 80% of complete response (CR) (16/20), 20% of partial response (PR) (4/20) and 100% of overall response were found in hsIMRT group, and 79.2% of CR (19/24), 20.8% of PR (5/24) and 100% of overall response were found in csIMRT group. For lymph node lesion, 75% (15/20) of CR and 25% (5/20) of PR were observed in hsIMRT group while 45.8% (11/24) of CR rate and 37.5% (9/24) PR in csIMRT group. Though differences in PR between two groups displayed no statistical significance (χ^2=1.93, P>0.05), those in CR were statistically significant (χ^2=3.84, P < 0.05).

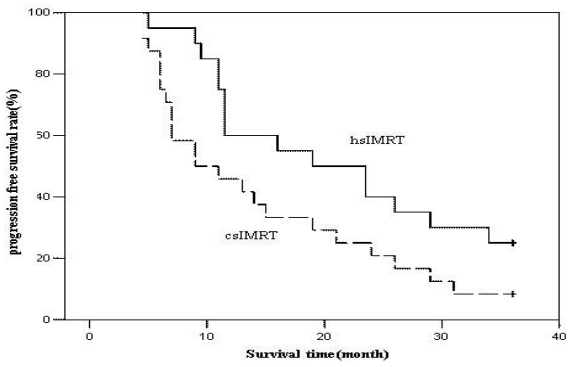

Figure 2. The Overall Progression-free Survival Curves of hsIMRT Group and csIMRT Group. The overall survival rate of 1-, 2- and 3-year was 60%, 40% and 25% in hsIMRT group, and 41.7%, 25% and 8.3% in csIMRT group, respectively, displaying statistically significant differences (χ^2=4.11, P < 0.05)

Survival rate

All the patients were followed up for 3 years with a rate of 100%. Though 1-, 2- and 3-year overall survival rates were 65%, 50% and 35% in hsIMRT group, and 58.3%, 37.5% and 25% in csIMRT group, displaying no statistically significant differences (χ^2=1.024, P>0.05) (Figure 1), the differences in 1-, 2- and 3-year relapse-free survival rates were of statistical significance (60%, 40% and 25% in hsIMRT group while 41.7%, 25% and 8.3% in csIMRT group, χ^2=4.11, P < 0.05) (Figure 2).

Discussion

Esophageal carcinoma is one of the most common diseases in China. For patients with neck or upper thoracic esophageal carcinoma, radiotherapy is a major treatment method now. Esophageal carcinoma is often accompanied with supraclavicular or superior mediastinal lymph node metastasis, and correlated with poor prognosis (Kawahara et al., 1998; Kurokawa et al., 2003; Xiao et al. 2003; Xiao et al., 2005; Tachimori et al., 2011) Research showed that IMRT technique can not only elevate target dose, but possesse advantages of higher target conformity, higher dose uniformity and better protection of sensitive organs compared with conventional conformal radiotherapy (Nutting et al., 2001; Fu et al., 2004; Wu et al., 2004; Chandra et al., 2005; Wang et al., 2006; Fenkell et al., 2008). It was reported 5~7 intensity-modulated beams were more effective in target dose uniformity, target conformity and radiation dose to organs at risk when comparing the effect of IMRT with that of 3D-CRT on 5 cases of upper esophageal carcinoma using simultaneous integrate boost (Fu et al., 2004). However, both IMRT and 3D-CRT have their limitations in treatment of esophageal carcinoma. For IMRT, dose verification has to be done for each patient, which is inevitably of great consumption of manpower and material resources. While for 3D-CRT, due to great differences in distance from the epidermis to the tumor between cervical esophagus and upper thoracic esophagus, the target dose is difficult to well distribute in the conventional or three-dimensional conformal radiotherapy. Therefore, in this study, simplified intensity modulated radiation therapy (sIMRT) was adopted in treating neck and upper thoracic esophageal carcinoma. According to the definition given by Tumour Hospital of Chinese Academy of Medical Sciences, sIMRT was an intensity-modulated radiotherapeutic technique with the average number of segments per beam ≤ 5, the segment area ≥ 10 cm^2 and the machine monitor for each segment ≥ 10 MU. Because parameters (such as the area, number of monitor unites of each segment, etc.) were close to those for 3D-CRT, the treatment verification procedure could be set as that of 3D-CRT except the dosimetric verification for each sIMRT plan due to its try-out period at present.

In this study, the difficulties in treating neck and upper thoracic esophageal carcinoma as well as the special advantage of intensity-modulated radiotherapy in dose distribution were taken into full consideration. In response to the difficulty in controlling metastatic lymph nodes, fractionation regimen of radiotherapy with higher doses were respectively given to PGTVnd and PTV1 (68.1Gy totally, 2.27Gy/fraction; and 63.9Gy, 2.13Gy/fraction, respectively) compared to conventional fractionation (1.8~2.0Gy/fraction). The treatment was completed within 6 weeks and the therapeutic time was shortened, which could undoubtedly increase the curative effect biologically. For CTV2 (volume in low risk), the regimen of 1.8Gy was adopted to decrease long-term radiation damage and increase the quality of life. The results indicated that the effect of hsIMRT on short-term survival rate was better than that of csIMRT. By improving CR of metastatic lymph nodes, hsIMRT can increase local tumor control, and thus promote the relapse-free survival rate. In addition, sIMRT has reduced the number of segments and machine monitors of each segment by optimization, and thereby, cut down the therapeutic time. Furthermore, as the optimized segment area and number of machine monitors of each segment (≥ 10MU) for sIMRT are very close to those for 3D-CRT, sIMRT, unlike IMRT, doesn't need trivial and complicated verification procedures, which has simplified treatment process and saved manpower and material resources.

Our study demonstrated that high fractionated dosage had a good control effect on metastatic lymph nodes. As sIMRT is more advantageous in protecting the peripheral normal tissues than 3D-CRT or conventional radiotherapy, the concurrent chemotherapy didn't increase the related toxicities. In addition, as high dose was concentrated on metastatic lymph node regions, no case of radiation-induced advanced-stage tracheal injury or tracheal stenosis occurred in patients of the study. Till now, the application of 3D-CRT to esophageal carcinoma has been well reported, however, reports on the effect of IMRT on esophageal carcinoma are only found in a little literature. Thus, its application needs further explorations, and its long-term curative effect should be proved through larger-scale clinical trials and long-term follow-up.

In conclusion, the results of this study showed that in the treatment of esophageal carcinoma with metastatic lymph nodes, the adoption of sIMRT successfully avoided those trivial verification procedures in IMRT and simplified clinical treatment process. High radiotherapeutic dose to metastatic lymph nodes effectively improved the local control rate and survival rate and its clinical application

was safe. It is evident that the application values of sIMRT in treating other types of human malignancies deserved further attention.

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