Journal of BUON **17:** 512-516, 2012

ORIGINAL ARTICLE

Different radiation treatment in esophageal carcinoma: a clinical comparative study

Jian-cheng Li, Di Liu, Min-qiang Chen, Jie-zhoug Wang, Jun-qiang Chen, Fei-yu Qian, Cheng Chen, He-Ping Zhang, Jian-ji Pan

Department of Oncology, Fujian Cancer Hospital, Fuzhou, The Teaching Hospital of Fujian Medical University, Fuzhou, Fujian, P.R. China

Summary

Purpose: *Conventional fractionation radiation therapy (CFRT), 3-dimensional conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT), are always applied to treat esophageal carcinoma. The purpose of this study was to analyse the therapeutic results and acute radiation side effects of radiotherapy in the treatment of esophageal carcinoma.*

Methods: *From March 2008 to May 2010, 117 patients with esophageal carcinoma treated at our hospital were included into this study. Thirty-eight (32.48%?) patients were treated with CFRT, 32 with 3DCRT and 47 with IMRT. The data were retrospectively collected and analysed.*

Results: *The objective response rates (complete/CR plus partial response/PR) in the CFRT group, 3DCRT group and IMRT group were 96.88, 92.11, and 91.49%, respectively ($p=0.617$). Furthermore, the one-year survival of the 3 groups was 77.9, 87.5 and 86.7%, respectively ($p=0.193$), and the 2-year survival 38.6, 55.1 and 57.7%, respectively ($p=0.211$). The incidence of acute radiation esophagitis in the IMRT+3DCRT groups was significantly higher compared with the CFRT group ($p=0.012$) and the incidence of acute radiation-induced pneumonitis, bronchitis and myelosuppression in the IMRT+3DCRT groups were lower compared with the CFRT group ($p<0.01$, $p=0.028$, and $p=0.01$, respectively).*

Conclusion: *Both IMRT and 3DCRT methods can improve the clinical therapeutic outcome of patients with esophageal carcinoma and decrease the incidence of acute radiation pneumonitis, radiation bronchitis and bone marrow suppression.*

Key words: acute toxicity, esophageal carcinoma, radiation therapy, survival

Introduction

The incidence of esophageal carcinoma is rising rapidly in the last 20 years [1,2]. Except eastern Europe, most Western industrialized countries but also Asian areas have similar developing trends of incidence [1,3]. Radiation therapy is one of the main treatment modalities for esophageal carcinoma [1,4-6]. Due to failure of local control, the curative effect of traditional CFRT of esophageal cancer has not increased significantly over the past few decades, with 5-year survival rate ranging only from 8 to 16% [7,8]. Furthermore, another important reason of poor efficacy is that many patients have advanced disease and larger tumor size on presentation. Conventional three-field isocentric irradiation technology makes it possible to deliver a high dose to the part of the tumor in the low dose area [9,10]. Consequently, the radiation fields must be expanded, which could lead to increased incidence of acute radiation side effects, such as radiation pneumonitis and leukopenia.

Improving the efficacy and long-term survival of patients with esophageal carcinoma is another problem to be answered. In recent years, 3DCRT and IMRT are gradually been adopted in clinical practice [11-13], as they can protect the surrounding normal organs and tissues at risk. Yet, the accuracy of target volume has not improved. Compared with CFRT, it is yet unclear whether 3DCRT and IMRT have specific positive impact on the patients' rehabilitation. Therefore, we had followed 117 patients with esophageal carcinoma in our hospital who were subjected to different radiotherapy techniques and their data are summarized in present study.

Correspondence to: Jian-cheng Li, MD, PhD. Fujian Cancer Hospital, Teaching Hospital of Fujian Medical University, Fuzhou, Fujian 350014, P.R. China. Tel/Fax: +86 0591 83660063, E-mail: jianchengli6@163.com

Received 03-10-2011; Accepted 12-12-2011

Methods

Patient and disease characteristics

From March 2008 to May 2010, 117 patients (median age 59 years, range 39-82) with pathologically confirmed esophageal carcinoma were staged and treated at the Fujian Provincial Cancer Hospital. Five cases (4.27%) had stage II disease, 53 (45.30%) stage III, and 59 (50.43%) stage IV. All patients had squamous cell carcinoma. Thirty-eight (32.48%) patients received CFRT, 32 (27.35%) received 3DRT, and 47 (40.17%) were subjected to IMRT (Table 1).

Radiotherapy

All patients were immobilized in supine position with neck and shoulder thermoplastic mold or thoracic vacuum pad plus body thermoplastic mold that were individually made in the desired position. Patients in the CFRT group were positioned in the CT simulator. Portal fields included demonstrable tumor lesion with 3 cm superior, 3 cm inferior, and 0.5-1 cm around the primary tumor. If the lesions were located in the cervical and upper thoracic esophagus, we performed prophylactic radiotherapy to bilateral lower neck and supraclavicular lymph nodes. However, patients who were treated with 3DCRT and IMRT were positioned in the CT simulator. Scan range was from C2 to L4, and both slice thickness and layer distance were 5 mm. According to ICRU report No. 50 [14] and No. 62 [15] about irradiation target, two doctors must be in charge of the target volume. Gross tumor volume (GTV) included patients with esophageal wall thickness > 5 mm, and short-diameter lymph nodes near the paraesophageal and tracheoesophageal groove and the pericardium > 0.5 cm. The clinical target volume (CTV) included the primary tumor with 0.5-0.8 cm near the tumor plus a margin of 3 cm around the primary tumor. Due to position error and moving target, the plan target volume (PTV) was the CTV plus a 3D margin of 0.5 cm. Dose daily fractions were 1.8-2.0 Gy, 5 days per week, up to a total dose of 60-66 Gy. The total treatment time ranged from 6 to 6.6 weeks and all patients completed their therapy.

Evaluation of side effects and survival

Acute radiation side effects were assessed and monitored using the National Cancer Institute Common Toxicity Criteria (V.CTC 3.0) and included radiation-induced nausea/vomiting, esophagitis, pneumonitis, bronchitis and bone marrow suppression. Short-term therapeutic effects were evaluated using the Chinese criteria [16]. One- and 2-year survival rates were calculated from the date of diagnosis.

Statistical analysis

All data were analysed using PASW Statistics v.18. The survival rates were assessed by chi-square test, and presented using the Kaplan-Meier method. Data was expressed as mean ± standard deviation (SD) or standard error of the mean (SEM). Statistical comparisons were carried out using Student's t test and ANOVA method.

Results

Patient follow-up

The follow-up time was from March 2008 to May 2010 (median 13 months, range 9-26). The follow-up rate was 94.74% and 93.75% for the CFRT and 3DCRT, respectively, while for the IMRT group it was 97.87%.

Symptom relief

Pain relief in the 3DCRT+IMRT groups was 90.9% (10/11) and 84.6% (11/13) in the CFRT group ($p>0.05$). Other disease symptoms (vomiting, dysphagia, weight loss) disappeared with treatment.

Table 1. Patient and tumor characteristics in the 3 radiotherapy groups

Groups	*CFRT N (%)*	*3DCRT N (%)*	*IMRT N (%)*	x^2	*p-value*
Patients, N	38 (32.48)	32 (27.35)	47 (40.17)		
Gender				4.270	0.118
Male	32 (27.35)	27 (23.08)	32 (27.35)		
Female	6 (5.13)	5 (4.27)	15 (12.82)		
Age (years)				0.460	0.794
>60	15 (12.82)	14 (11.97)	22 (18.80)		
≤60	23 (19.66)	18 (15.38)	25 (21.37)		
Tumor location				6.095	0.413
Cervical	1 (0.85)	0 (0)	3 (2.56)		
Upper thoracic	13 (11.11)	7 (5.98)	8 (6.84)		
Middle thoracic	21 (17.95)	22 (18.80)	30 (25.64)		
Lower thoracic	3 (2.56)	3 (2.56)	6 (5.13)		
Clinical stage*				11.289	0.024
I	0 (0)	0 (0)	0 (0)		
II	4 (3.42)	1 (0.85)	0 (0)		
III	15 (12.82)	20 (17.09)	18 (15.38)		
IV	19 (16.24)	11 (9.40)	29 (24.78)		

*3DCRT and IMRT: p=0.037; 3DCRT and CFRT: p=0.125; IMRT and CFRT: p=0.065

Local disease control

In the CFRT group there were 16, 15, 1 and 0 patients with CR, PR, SD and PD, respectively. In the 3DCRT the corresponding figures were 18,17,2 and 1; in the IMRT group these figures were 23,20,4 and 0, respectively.

Local disease control is shown in Table 2. CR plus PR rates of CFRT, 3DCRT and IMRT groups were 96.88, 99.11 and 91.49%, respectively (p=0.617).

Survival

As shown in Figure 1, the 1-year survival rate of CFRT, 3DCRT and IMRT groups was 77.9, 87.5 and 86.7%, respectively (p=0.193); the 2-year survival rate was 38.6, 55.1 and 57.7%, respectively (p=0.211). Median survival of the 3 groups with 95% CI is shown in Table 3.

Acute radiation-induced effects on normal tissues

As shown in Table 4, there were statistically significant differences between the patients of the 3 radiation groups concerning radiation-induced esophagitis, pneumonitis, bronchitis and myelosuppression.

Table 2. Objective response in local disease

Groups	*CR+PR N (%)*	*SD+PD N (%)*	x^2	*p-value*
CFRT	31 (96.88)	1 (3.12)	0.966	0.617
3DCRT	35 (92.11)	3 (7.89)		
IMRT	43 (91.49)	4 (8.51)		

For abbreviations see text

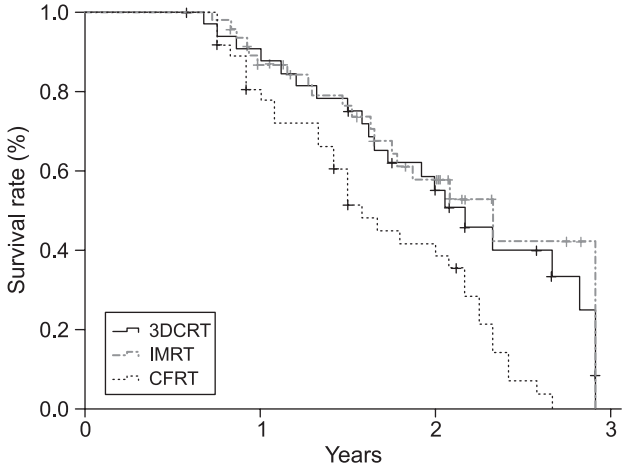

Figure 1. Survival according to the 3 radiotherapy methods.

Table 3. Median survival time according to the different radiotherapy groups

Radiation treatment	*Median survival (years)*	*95% confidence interval*	*p-value*
3DCRT	2.17	1.76-2.58	0.012
IMRT	2.33	1.64-3.02	
CFRT	1.58	1.24-1.92	

For abbreviations see text

Table 4. Comparison of acute radiation side effects on normal tissues

Side effects	*CFRT N (%)*	*3DCRT N (%)*	*IMRT N (%)*	x^2	*p-value*
Number of cases	38 (100)	32 (100)	47 (100)		
Esophagitis				8.849	0.012
Yes	15 (39.5)	22 (68.8)	32 (68.1)		
No	23 (60.5)	10 (31.2)	15 (31.9)		
Pneumonitis				18.584	<0.010
Yes	15 (39.5)	4 (12.5)	2 (4.3)		
No	23 (60.5)	28 (87.5)	45 (95.7)		
Bronchitis				7.144	0.028
Yes	12 (31.6)	4 (12.5)	5 (10.6)		
No	26 (68.4)	28 (87.5)	42 (89.4)		
Leukopenia				9.212	0.010
Yes	9 (23.7)	1 (3.1)	3 (6.4)		
No	29 (76.3)	31 (96.9)	44 (93.6)		

For abbreviations see text

Discussion

Esophageal cancer has become one of the most common cancers in China, and ranks 4th in incidence and mortality among malignant diseases [19,20]. Most patients with esophageal cancer are diagnosed with advanced and inoperable disease at first presentation. In addition, more than 90% of the cases are squamous cell carcinomas, which are sensitive to radiation, thus currently radiation therapy is the principal, effective and safe method for the treatment of this malignancy [21,22]. About 80% of patients with esophageal cancer are treated with radiation therapy or combined radiotherapy plus chemotherapy or by surgery and 20% of patients are treated with chemotherapy alone [17]. Survival after CFRT has not increased significantly over the past years and 5-year survival has remained at 8-16% [14]. In 1980, the Chinese Academy of Medical Sciences Tumor Hospitals reported on 3798 cases with esophageal carcinoma treated with radiotherapy; the 5-year survival rate was only 8.4% [23]. Owing to vital organs at risk, including the spinal cord and lung, and their limited tolerance to radiation, it is difficult to deliver CFRT in order to increase the target dose. In our study local recurrence was the main reason of failure, mainly due to underdosing and poor dose uniformity in

CFRT. In recent years, with the progress of diagnostic techniques such as CT, MRI, and PET-CT, and advances in radiotherapy equipment and technology, quite a number of more precise radiotherapeutic techniques emerged, including 3DCRT and IMRT, which make it possible to achieve high and uniform dose, and also to reduce the target volume and dose to normal tissues at risk. Fenkell et al. [24] analyzed the treatment plan and dosimetry of 10 cases of esophageal cancer in 2008 and suggested that 3DCRT can increase the radiation dose to 5-10 Gy to esophagus; however, this method did not increase the total mean dose to the lung. Therefore, under these conditions, employing 3DCRT can improve the local control rate by 15-25%. However, whether there are other benefits compared with CFRT is unclear.

The results of our study showed that most of the patients achieved CR and PR in the short-term, and the local control rates displayed no significant difference among the 3 different radiation methods used ($p > 0.05$). Reports from China show 5-year survival rate ranging from 5 to 9%. In 500 patients from China with esophageal cancer who received CFRT, the 1-year survival rate was 71.9% [25], and the 1-, 2-, 3-, and 4-year survival rates after CFRT were 49.1, 41.1,30.4, and 22.3%, respectively [26]. However, the 1-year survival rate of CFRT, 3DCRT and IMRT groups in the present study was 77.9, 87.5, and 86.7%, respectively, and the 2-year survival rate was 38.6, 55.1, and 57.7%, respectively. The 1- and 2-year survival rates of 3DCRT and IMRT groups were significantly higher compared with the CFRT group ($p<0.05$), indicating that 3DCRT and IMRT could improve survival.

All toxicities between CFRT and 3DCRT or IMRT were statistically different ($p<0.05$). Due to the higher tumor dose distribution and different target volume, the incidence of radiation-induced esophagitis in the 3DCRT and IMRT groups was significantly higher than in the CFRT group ($p<0.05$). However, the irradiation dosage to the surrounding normal tissues was significantly reduced in the 3DCRT and IMRT groups compared with the CFRT group. It is our practice to suggest patients to eat soft, liquid or semi-liquid food and administer mucosal protective agents, like vitamin A, during treatment to effectively reduce the incidence of radiation-induced esophagitis. For patients who show signs of radiation-induced esophagitis, we use prophylactic anti-inflammatory and analgesic drugs. In addition to esophageal mucosa, other normal tissues can be protected in 3DCRT or IMRT [27]. Myelosuppression was significantly milder in the IMRT and 3DCRT groups compared with CFRT group, obviously due to the better conformal radiation in 3DCRT and IMRT groups, resulting in low radiation dose to the spinal cord.

Lung is often subjected to radiation with certain doses, which result in different degrees of radiation injury. IMRT and 3DCRT can reduce the incidence of radiation pneumonitis by reducing the radiation dose to the lung by improving the homogeneity of the target volume [28]. In our study, less radiation pneumonitis was registered in the IMRT and 3DCRT groups compared to CFRT group ($p<0.05$). The IMRT and 3DCRT techniques are advantageous in that the shape of high-dose region is similar to the shape of the target volume in 3D. Furthermore, the dose outside the target decreased rapidly in order to increase the radiation tumor dose and dose uniformity, which could effectively protect the surrounding normal tissues and organs [29].

In conclusion, local control rates of 3 groups were equal. However, the 1- and 2-year survival rate of the 3DCRT and IMRT group were higher compared to CFRT group. Except radiation esophagitis, the other acute radiation side effects in the 3DCRT and IMRT groups were lower than those in the CFRT group. Moreover, we concluded that there was no significant difference in acute radiation side effects between the 2 new radiotherapy techniques - 3DCRT and IMRT. Our results also indicated that 3DCRT or IMRT can reduce the acute radiation side effects, contributing thus to improved quality of life, and improve the therapeutic effect of radiotherapy (better 1- and 2- year survival). It is worth testing these two new radiation techniques since their superiority has not been fully assessed so far, making it necessary to confirm their value in large randomized clinical trials.

Acknowledgements

This work was supported by Fujian Provincial Health Innovation project of China (2007-CX-4).

References

1. Bollschweiler E, Wolfgarten E, Gutschow C et al. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer 2001; 92: 549-555.
2. Pera M, Manterola C, Vidal O et al. Epidemiology of esophageal adenocarcinoma. J Surg Oncol 2005; 92: 151-159.
3. Milenic DE, Brady ED, Brechbiel MW. Antibody-targeted radiation cancer therapy. Nat Rev Drug Discovery 2004; 3: 488-499.
4. Devesa SS, Blot WJ, Fraumeni Jr JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998; 83: 2049-2053.
5. Brücher BLDM, Stein HJ, Bartels H et al. Achalasia and esophageal cancer: incidence, prevalence, and prognosis. World J Surgery 2001; 25: 745-749.

6. Minsky BD, Pajak TF, Ginsberg RJ et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002; 20: 1167-1174.
7. Urba SG, Orringer MB, Turrisi A et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001; 19: 305-313.
8. Gu Y, Swisher SG, Ajani JA et al. The number of lymph nodes with metastasis predicts survival in patients with esophageal or esophagogastric junction adenocarcinoma who receive preoperative chemoradiation. Cancer 2006; 106: 1017-1025.
9. O'Donnell C, Fullarton G, Watt E et al. Randomized clinical trial comparing self-expanding metallic stents with plastic endoprostheses in the palliation of oesophageal cancer. Br J Surgery 2002; 89: 985-992.
10. Hage M, Siersema PD, Dekken H et al. Oesophageal cancer incidence and mortality in patients with long-segment Barrett's oesophagus after a mean follow-up of 12.7 years. Scand J Gastroenterol 2004; 39: 1175-1179.
11. Chandra A, Liu H, Tucker S et al. IMRT reduces lung irradiation in distal esophageal cancer over 3D CRT. Int J Radiat Oncol Biol Phys 2003; 57: S384-S385.
12. Wu V, Sham J, Kwong D. Inverse planning in three-dimensional conformal and intensity-modulated radiotherapy of mid-thoracic oesophageal cancer. Br J Radiol 2004; 77: 568-572.
13. Chandra A, Guerrero TM, Liu HH et al. Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer. Radiother Oncol 2005; 77: 247-253.
14. Kelsen DP, Ginsberg R, Pajak TF et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998; 339: 1979-1984.
15. Delcambre C, Jacob JH, Pottier D et al. Localized squamous-cell cancer of the esophagus: retrospective analysis of three treatment schedules. Radiother Oncol 2001; 59: 195-201.
16. Stroom JC, Heijmen BJM. Geometrical uncertainties, radiotherapy planning margins, and the ICRU-62 report. Radiother Oncol 2002; 64: 75-83.
17. Wjxag SZ. Curative effect evaluation criteria of esophageal carcinoma after radiotherapy. Chinese J Radiat Oncol 1989; 3: 3-7 (in Chinese).
18. Hayman JA. Treatment summaries in radiation oncology and their role in improving patients' quality of care: past, present, and future. J Oncol Pract 2009; 5: 108-109.
19. Notani PN. Global variation in cancer incidence and mortality. Curr Sci 2001; 81: 465-474.
20. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol 2001; 2: 533-543.
21. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. CA: Cancer J Clinicians 2005; 55: 74-108.
22. Allum W, Griffin S, Watson A et al. Guidelines for the management of oesophageal and gastric cancer. Gut 2002; 50: 1449-1472.
23. Komaki R, Moughan J, Ettinger D et al. Acute esophagitis correlated with irradiated volume in a phase II study of accelerated high dose thoracic radiation therapy (TRT) with concurrent chemotherapy for limited small cell lung cancer (LSCLC) (RTOG 0239): P1-205. J Thor Oncol 2007; 2: S819-820.
24. Fenkell L, Kaminsky I, Breen S et al. Dosimetric comparison of IMRT vs. 3D conformal radiotherapy in the treatment of cancer of the cervical esophagus. Radiother Oncol 2008; 89: 287-291.
25. Ywzlyze Al. Clinical analysis of 3798 cases of radiotherapy of esophageal carcinoma. China Oncology 1980; 2: 5-9 (in Chinese).
26. Zslwye Al. 500 cases of advanced esophageal carcinoma with radiotherapy alone in multivariate analysis. Chin J Radiat Oncol 2005; 7: 7-10 (in Chinese).
27. Zimmermann FB, Geinitz H, Feldmann HJ. Therapy and prophylaxis of acute and late radiation-induced sequelae of the esophagus. Strahlenther Onkol 1998; 174 (Suppl 3): 78-81.
28. Cohen RJ, Paskalev K, Litwin S et al. Esophageal motion during radiotherapy: quantification and margin implications. Dis Esophagus 2010; 23: 473-479.
29. Welsh J, Palmer MB, Ajani JA et al. A Esophageal Cancer Dose Escalation using a Simultaneous Integrated Boost Technique. Int J Radiat Oncol Biol Phys 2012; 82: 468-474.