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Original Article

Analysis of different fractionations of three-dimensional conformable radiotherapy for esophageal cancer

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Abstract: This study aims to observe and discuss the curative and side effects of three different fractionation regimen of three-dimensional conformable radiotherapy (3DCRT) for esophageal cancer. A total of 169 untreated patients of esophageal cancer were randomized into three groups: groups A (conventional group, 2.0 Gy per time), B (2.5 Gy group, 2 Gy per time), and C (3.0 Gy group, 3.0 Gy per time), respectively. Groups A, B, and C are similar in terms of partial response ($P = 0.35$). However, the three groups had no significant differences in terms of the complete response ($P = 0.63$). The three-year survival rate of group B was higher than those of the other two groups, and the difference was significant ($P = 0.047$). For the three-year local control rate, that of group B was also higher than those of groups A and C, but the difference was not significant ($P = 0.067$). The incidence rate of 3 level esophagitis and bronchitis was highest in group C ($P = 0.023$ and $P = 0.064$). The 3 level tardive radioactive esophagitis in group C was higher than those in other two groups ($P = 0.037$ and $P = 0.04$). The incidence rate of the 3 level advanced lung reaction was also the highest in the three groups ($P = 0.041$). The effect is better and the side effect is tolerable for the 2.5 Gy per fraction, 5 times per week; thus, it can be used clinically for 3DCRT for esophageal carcinoma.

Keywords: Carcinoma, esophageal/radiotherapy, radiotherapy, three-dimensional conformal, fractionation

Introduction

Esophageal cancer is the fourth leading cause of cancer death and accounts for 16.4% of the cancer deaths in China. Surgery remains the first preferred means of curative method for patients who are fit for resection. Meanwhile, radiotherapy is one of the main treatment methods of esophageal carcinoma for those who are unfit for resection or adjuvant patients. However, the effect of conventional radiotherapy is unsatisfactory. Most of the references reported that the five-year survival rate of radiotherapy alone is less than 10%, whereas local failure still remains the main reason for radiotherapy. For conventional treatment, the main limitation to the dose escalation is the target volume and the adjacent organ at risk (OAR). Thus, the fractionation of 1.8 Gy to 2.0 Gy remains the standard fractional dose for conventional radiotherapy. The development of accurate radiotherapy technology provides the condition for observing the effect of different dose fractionations. In our study, we analyzed the difference of three dose fractionations in three-dimensional conformable radiotherapy (3DCRT) to provide guidance for clinical treatment.

Materials and methods

Eligibility criteria

All esophageal cancers were identified with untreated and histological. Both esophageal adenocarcinoma and squamous cell cancers were included in the trial. The age of the patients was < 15 years, and the Karnofsky performance status scales were ≥ 70. Patients who had synchronous or history of other malignancies, distant metastasis or esophageal perforation, and bleeding or esophageal cancer length of more than 9 cm were excluded. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First Hospital of Shijiazhuang City. Written informed consent was obtained from all participants.

Table 1. The clinical data distribution and comparability of three groups

	Group A	Group B	Group C	χ^2 value	*P* value
No. of Patients	56	56	57		
Gender					
Male	36	35	34	0.26	0.88
Female	20	21	23		
Age in years (range)					
40-55	24	23	25	0.09	0.95
55-74	32	33	32		
Cancer type					
Esophageal carcinoma	42	43	40	0.69	0.70
Esophageal adenocarcinoma	14	13	17		
Site					
Upper	17	16	16	0.12	0.94
Middle	29	28	30		
Lower	10	12	11		
Length (cm)					
< 5	19	17	18	0.43	0.79
5-7	25	26	28		
> 7	12	13	10		

Table 2. The comparative of short term effect No. of patient (%)

	Group A	Group B	Group C	χ^2 value	*P* value
No. of Patients	56	56	57		
Complete remission CR	42 (75)	45 (80)	44 (77)	0.91	0.63
Partial remission PR	11 (20)	9 (16)	10 (17)	0.10	0.95
No respond to treatment	3 (5)	2 (4)	3 (5)	2.92	0.24
Effective (CR + PR)	53 (95)	54 (96)	54 (95)	2.33	0.35

Clinical characteristics

A total of 169 patients with esophageal carcinoma who had undergone 3DCRT between January 1, 2005 and March 30, 2007 were selected in the trial. The patients were randomized into three groups: A, B, and C. No significant difference was observed in terms of clinical characteristics (**Table 1**).

Therapeutic method

The patient's location was fixed with a shrink film and a positioning plate; correct positioning is very important. All patients underwent computed tomography (CT) simulation. The position of the tumor was fixed using a CT simulation machine, and the information of the tumor was transferred to a computer. The patients were immobilized using a customized vacuum-locked cradle. The gross tumor volume (GTV), including tumor and lymph nodes with sizes larger than 1 cm, was defined as any visible tumor on the image. Clinical target volume was defined as the GTV plus a 1.5 cm to 2.0 cm margin, and the planning target volume was defined as the clinical target volume plus a 0.3 cm to 0.5 cm margin. Radiotherapy planning was designed, and the dose distribution was adjusted by a physiotherapist. The dose limitations of the OARs were as follows: the mean dose of all-lung was less than 12 Gy and V_{20} < 30%; the dose of the spinal cord (any point) was less than or equal to 43 Gy; and the mean dose of the heart was less than 26 Gy. Group A, conventional treatment group, 2.0 Gy per time, 5 times per week, and 30 to 33 times in total. Group B, 2.5 Gy per time, 5 times per week, and 21 to 23 times in total. Group C, 3.0 Gy per time, 3 times per week, and 16 to 18 times in total. The total dose was 60 Gy to 66 Gy. The average doses were 63.5 Gy, 64 Gy, and 63.8 Gy, respectively. Based on the LQ and the TDF genes, the equal effect biology dosage conversion was practiced in the non-routine group. After the completion of the treatment plan, the position was readjusted using a simulation machine. The patients were treated with radiation therapy by using a 6 MV SIEMMNS PRIMUS H electron linear accelerator. After the end of the radiotherapy treatment for 15 days, all patients were treated with four consecutive cycles of chemotherapy. One cycle lasted for 28 days. The treatment plan is as follows: PDD, 25 mg/m^2 to 30 mg/m^2, from the first to the fifth day; and 5-Fu, 450 mg/m^2 to 500 mg/m^2, from the first to the fifth day. The blood routine of the patients was checked 1 to 2 times, and the liver and renal functions were also checked each time during the treatment.

Table 3. The comparative of long term effect No. of patient (%)

	Group A	Group B	Group C	χ^2 value	*P* value
No. of Patients	56	56	57		
Local control rate					
1-year	42 (75)	45 (80)	47 (83)	1.008	0.604
2-year	37 (66)	39 (70)	38 (67)	0.186	0.911
3-year	20 (36)	32 (57)	29 (51)	5.419	0.067
Survival rate					
1-year	44 (79)	48 (86)	48 (84)	1.112	0.574
2-year	32 (57)	41 (73)	37 (65)	3.165	0.205
3-year	20 (36)	32 (57)	22 (39)	6.128	0.047

Evaluation criterion

All patients were tolerant to the treatment. After finishing the treatment, a follow-up was performed once every three months. The local control and distant metastasis would be observed via CT, B-mode ultrasonic, and fiber-optic bronchoscopy. After three months of complete radiation therapy, we evaluated the condition of the patients. The short-term effect was evaluated using an objective standard. The acute toxicity was evaluated using the RTOG criterion. Late toxicity was evaluated using the RTOG/EORTC criterion.

Statistical analysis

The SPSS 17.0 software was adopted to perform the statistical analysis. The comparison of the clinical data, short-term effect, and side effect were analyzed with the χ^2 test and analysis of variance. The local control rate and the survival rate were calculated using the Kaplan-Meier and log-rank tests.

Results

Completion status treatment and follow-up

During the treatment, 8 patients with severe adverse toxicity underwent hormone and antibiotic therapies. The follow-up was completed until September 2009. During the follow up period, 2 patients were lost, and the follow up rate was 98.8%.

Short term effect

The rates of partial response was similar in the three groups, which were 95%, 96%, 95%, respectively, but no significant difference was observed (χ^2 = 2.33, *P* = 0.35). No significant differences were observed for the rate of complete response between the three groups (75%, 80%, and 77% respectively, χ^2 = 0.91, *P* = 0.63). However, the CR of group B was slightly higher than those of the other two groups (**Table 2**).

Long-term effect

The survival results were analyzed using the Kaplan-Meier and log-rank tests. The three-year survival rate of group B was higher than those of the other two groups, with significant difference (χ^2 = 6.128, *P* = 0.047). Group B was also higher than groups A and C in terms of the local control rate of three years, but the difference was not significant (χ^2 = 5.419, *P* = 0.067) (**Table 3**).

Figure 1 shows the local control rate for three years of the three groups, and **Figure 2** shows the survival rate.

Comparisons of the course of radiotherapy

The times of radiotherapy in the three groups were (44 ± 3), (30 ± 3), and (23 ± 3) days, respectively. The time of group A was longer than those of groups B and C.

Treatment response

The early responses are listed on **Table 4**. Other results are listed in **Table 5**. One patient in group B developed esophageal perforation (1.8%). In group C, two patients developed esophageal perforation, and one developed esophageal variceal bleeding (5.3%).

In group A, 25 patients died of tumor recurrence, and 11 patients died of tumor metastasis. In group B, 11 patients died of tumor recurrence, 13 patients died of tumor metastasis, and 1 patient died of esophageal perforation. In group C, 13 patients died of tumor recurrence, 19 patients died of tumor metastasis, 2 patients died of esophageal perforation, and 1 patient died of esophageal variceal bleeding.

Discussion

Radiotherapy is a very important method for treating advanced esophageal carcinoma in

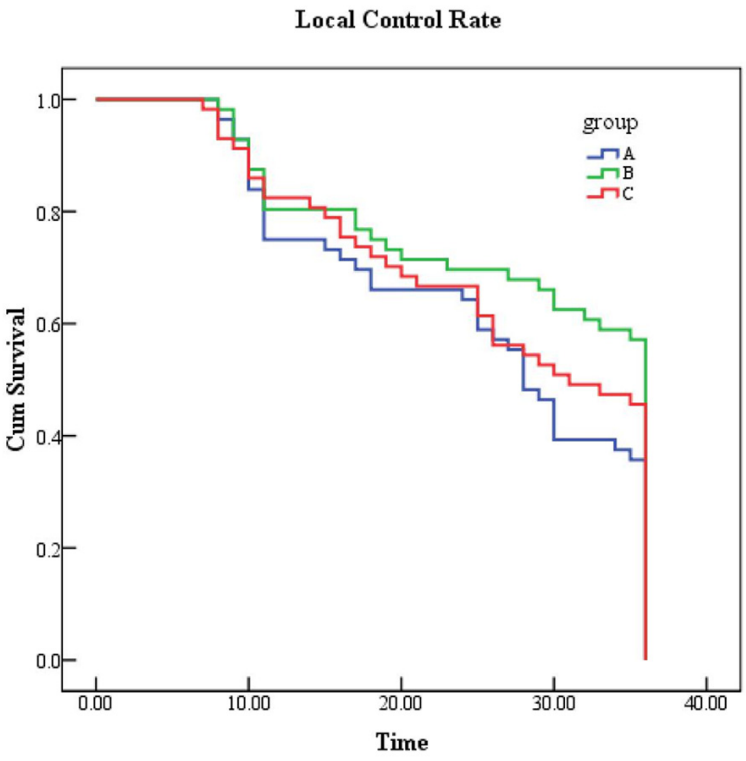

Figure 1. The PR rate of three groups.

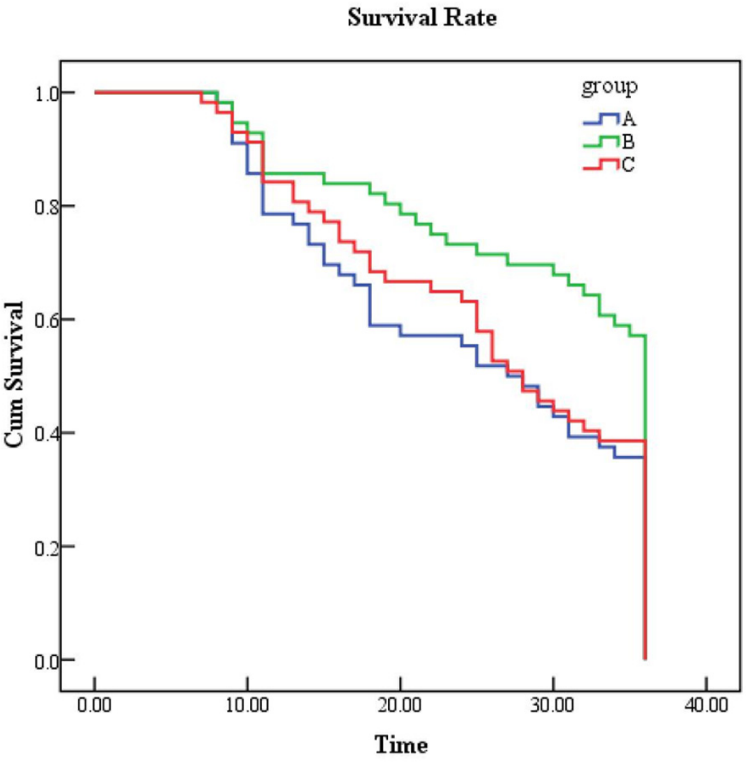

Figure 2. The survival rate of three groups.

patients who are unfit for surgery. However, the clinical efficacy of radiotherapy for esophageal carcinoma still remains unsatisfactory. The five-year survival rate is only about 10% for two-dimensional conformal radiotherapy [1-3]. The main reason of treatment failure after radiotherapy is tumor residue, which accounts for 75% to 96% [4, 5]. Thus, the increase in the local control rate is the key to improving the survival rate. With the progress of radiobiology, the study of late course accelerated radiation for esophagus carcinoma has greatly progressed [6-10]. The dose distribution for conventional radiotherapy is uneven; thus, the damage of the normal tissue cannot be directly evaluated. In addition, the change in fractionation is limited. The development of precise radiotherapy makes the high-dose region consistent with the disease (target) in three dimensions, especially after 3DCRT became popular. 3DCRT can increase the tumor dose and decrease the normal tissue dose and as well as improve the local control rate and the survival rate for esophagus cancer patients [11-13]. Researchers made progress in developing a non-conventional fraction model [10, 14-17]; however, the best fractionation is still undetermined. Currently, the allocation of treatment time and dose has no uniform standard. In this study, none of the three fractions are better than the others in terms of their short-term effect. Three fraction doses have no significant difference in the one-year survival rate, one-year local control rate, two-year survival rate, and two-year local control

Table 4. The comparison of early responses No. of patient (%)

	Group A	Group B	Group C	χ^2 value	*P* value
No. of Patients	56	56	57		
Acute radiation esophagitis					
Stage I	27 (48)	30 (54)	27 (47)	0.25	0.88
Stage II	15 (27)	20 (36)	29 (52)	7.11	0.03
Stage III	2 (4)	5 (9)	11 (21)	7.60	0.023
Stage IV	0 (0)	0 (0)	0 (0)	0	1
Acute radiation pneumonitis					
Stage I	15 (27)	16 (29)	14 (25)	0.23	0.89
Stage II	9 (16)	15 (27)	21 (37)	6.23	0.041
Stage III	0 (0)	2 (4)	5 (9)	5.54	0.064
Stage IV	0 (0)	0 (0)	0 (0)	0	1

Table 5. The comparison of terminal responses No. of patient (%)

	Group A	Group B	Group C	χ^2 value	*P* value
No. of Patients	56	56	57		
Radiation esophagitis					
Stage I	19 (34)	24 (43)	28 (49)	2.7	0.26
Stage II	7 (13)	10 (18)	18 (32)	6.68	0.037
Stage III	2 (4)	5 (9)	10 (18)	6.25	0.04
Stage IV	0 (0)	1 (2)	3 (5)	3.51	0.19
Radiation pneumonitis					
Stage I	12 (21)	17 (30)	21 (37)	3.25	0.21
Stage II	5 (9)	9 (16)	11 (19)	2.52	0.28
Stage III	0 (0)	3 (5)	6 (11)	6.21	0.041
Stage IV	0 (0)	0 (0)	0 (0)	0	1

rate. The three-year survival in group B is much better than those in the other two groups. The three-year local control rate in group B is the best among the groups, but the difference has no statistical significance. The long-term effect in group B is better than those in groups A and C. With the extension of follow-up time, the advantage of group B is still more obvious.

Many research findings have revealed that the effect of tumor therapy is related to the total treatment time. The biological effects decreased with increasing course of radiotherapy. Several studies have reported that the rapid reproliferation of cancer cells occurred after four weeks from the beginning of radiotherapy [18]. In the present study, we selected two time-dose fractionations: group B with 2.5 Gy and group C with 3.0 Gy. The total course of radiotherapy was less than 35 days for each group. The total radiation dose reached a biologically effective dose in the conventional group. The tumor stem cells would be killed before they rapidly reproliferate. Thus, the treatment course is shortened.

This study shows that the incidence of the two-grade acute radiation esophagitis and acute radiation pneumonitis in group C is higher than those in the other groups. A significant difference was observed between groups A, B, and C. This finding suggests that the acute side reactions are more severe with increasing single dose. The incidence of the two-grade side effect on the esophagus in group C is also the highest. A significant difference was observed between groups A, B and, C. Two esophageal perforation and one esophageal variceal bleeding occurred during radiotherapy. The incidence of the three-grade toxicity in group C is obviously higher than those in the other groups, which indicates that the long-term side effects increased with increasing single dose, such as esophageal injury and lung injury. Thus, this condition must be given great importance.

In recent years, a consensus exists that individual comprehensive therapy as the current best treatment for carcinoma of esophagus at advanced stages. Wrong et al. supposed that concurrent chemoradiotherapy is more effective than single radiotherapy or sequential chemoradiotherapy [19]. However, concurrent chemoradiotherapy can increase the risk of several derived disease, such as radiation esophagitis, myelosuppression, nausea, and vomiting. The radiation esophagitis incidence rate is much higher with concurrent chemoradiotherapy by using DDP and 5-Fu. Seung et al. reported that the incidences of two- and three-grade acute esophagitis are 89% and 39%, respectively [20]. Considering the increase in side effects, we selected sequential chemora-

diotherapy because it was more comparable for three time-dose fractionation with concurrent chemoradiotherapy. When this method is used, the influence of chemotherapy would greatly be reduced.

In short, the patients' effect in group B is better than in the other two groups. This means that 2.5 Gy per time, 5 times per week, and 21 to 23 times in total is the best fractionation model in the three models. In addition, this treatment reduced the length of time, increased the precision of setup positioning, and decreased costs. We consider this model as one of the treatment models for esophageal cancer. In view of individual treatment, conventional division is the best way for patients with poor physical tolerance. The side effect in group C hardly improved, and the effect did not show any sign of progression. Consequently, the model of the fractionation in group C is unsuitable for esophageal cancer.

The 3DCRT and intensity modulated radiotherapy offer technical support for the investigation of time-dose division model. Thus, the application of these technologies has become an important research direction, which can help improve the long-term survival rate of esophageal cancer and can reduce the side effects. This article is an elementary discussion about this issue. The best method for time-dose fractionation still needs to be explored in the future.

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Disclosure of conflict of interest

None.

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