

Randomized clinical trial on seven-day-per-week continuous accelerated irradiation for patients with esophageal carcinoma: Preliminary report on tumor response and acute toxicity

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Abstract

AIM: Tumor response and normal tissue toxicity of seven-day-per-week continuous accelerated irradiation (CAIR) for patients with esophageal carcinoma were evaluated and compared to conventional irradiation (CR).

METHODS: Sixty patients with squamous cell carcinoma of the esophagus were randomized into two groups: the CAIR group (30 patients) and the CR group (30 patients). Patients in the CAIR group received radiotherapy (RT) with 2 Gy/fraction per day at 7 d/wk with a total dose of 50-70 Gy (average dose 64.2 Gy). The overall time of irradiation was 3.6-5.0 wk (average 4.6 wk). RT in the CR group was 2 Gy/fraction per day at 5 d/wk with a total dose of 40-70 Gy (average dose 61.7 Gy). The overall time of irradiation was 4.0-7.0 wk (average 6.4 wk).

RESULTS: The data showed that the immediate tumor response to RT was better in the CAIR group than in the CR group. Efficiency rates (CR plus PR) were 82.8% (24/29) and 58.6% (17/29), respectively ($P = 0.047$). In both groups the incidences of esophagitis and tracheitis were insignificant ($P = 0.376, 0.959$), and no patient received toxicity that could not be tolerated.

CONCLUSION: CAIR shortens overall treatment time and is well tolerated by patients. It may be superior to CR in enhancing the local response of tumor, but its remote effect for esophageal carcinoma awaits further follow-up.

INTRODUCTION

Esophageal carcinoma, especially in China, is one of the most common cancers. Its treatment results are rather dismal, with 5-year survival rates of about 5%-10% for conventional radiotherapy (CR)^[1,2]. The poor prognosis is the result of both, local residual disease and early disease relapse. Thus for esophageal carcinoma, local control is the most important factor in prolonging survival^[3]. Several animal experiments and clinical investigations have shown that accelerated repopulation of surviving tumor clonogens during a standard course of RT is one of the major reasons for treatment failure in several cancers^[4-6]. Some clinical trials of accelerated hyperfractionated RT have been carried out with the aim of overcoming this problem by shortening the overall treatment time. Some reports have already suggested improvement in local control and survival rates, but at the expense of increasing acute toxicity, particularly with the faster schedule^[6-8]. In recent years, another RT schedule has been used to treat head and neck cancer. The idea was simple-to continue radiation during the weekends. In this way, the overall treatment time has shortened for about two weeks, giving one fraction per day, seven days a week (including Saturday and Sunday), without any change of the other parameters as time or dose. This schedule was defined as a continuous accelerated irradiation (CAIR) and has been compared to conventional five days treatment in a randomized prospective study for head and neck cancer^[9]. Using this RT schedule, patients with esophageal carcinoma were treated and our study aimed to evaluate tumor response and normal tissue toxicity.

MATERIALS AND METHODS

Materials

From October 2003 to December 2005, 60 unresectable or medically inoperable patients with esophageal carcinoma were enrolled and randomized into two groups by the sealed envelope method. The project of clinical randomized trial on seven-days-per-week continuous accelerated irradiation (30 patients) *vs* conventional treatment (30 patients), including the criteria for patient eligibility, the diagnostic procedure, the randomization method, the fractionation schemes of treatment techniques, and patient care was approved by the Ethical Committee of Xuzhou Cancer Hospital. All patients received full information concerning the aim of the study, diagnostic and treatment procedures, medical care, risk of acute and late sequelae before they entered the trial. All patients gave informed consent to this study.

Only patients with histologically proven squamous cells of esophageal carcinoma were included in the trial. Additional criteria for eligibility were age ≤ 75 years, Karnofsky performance status ≥ 70 , white blood cell and hemoglobin levels within normal range, and no prior treatment. The pretreatment evaluation generally included chest radiography, chest CT scan, esophageal barium film, and ultrasound examination of the abdomen, including liver, kidney, spleen, and retroperitoneal lymph nodes, and liver and renal function tests. Based on examinations mentioned above, tumor staging was performed according to the TNM staging system of the 1997 American Joint Committee on Cancer staging system. Patients' characteristics are presented in Table 1 which shows comparable distribution of biological and clinical factors in both groups of the trial.

Methods

Radiation methods: Radiation source was 6MV-X-ray linear accelerator. For the design of the radiation fields for all patients, a three-field approach was used: one anterior and two posterior oblique portals. The length of the field should cover clinical tumors with 3 cm extended margin at both ends of the lesion. The width of the fields was adjusted to cover gross tumors with 2 cm margins to include the subclinical lesions. RT in CAIR group was 2 Gy/fraction per day for 7 d/wk with a total dose of 50-70 Gy (average dose 64.2 Gy), the overall time of irradiation was 3.6-5.0 wk (average 4.6 wk). RT in CR group was 2 Gy/fraction per day for 5 d/wk with a total dose of 40-70 Gy (average dose 61.7 Gy), the overall time of irradiation was 4.0-7.0 wk (average 6.4 wk).

Tumor response and acute radiation reactions evaluated: All patients received esophageal barium examination before, during, and at the end of RT. At the end of RT, the tumor response to RT was evaluated. A complete response (CR) was the disappearance of the mass shadow, no narrowing observed in the esophageal lumen, and no, or slight rigidity of the esophageal wall remains without residual ulceration. A partial response (PR) was a $> 50\%$ reduction in tumor bulk but $< 100\%$ resolution of the disease and a residual shallow ulcer with a diameter of < 1.5 cm, despite the disappearance of the mass shadow. A minor response

Table 1 Patients' characteristics

Characteristic	CAIR group	CR group	χ^2 or <i>t</i>	<i>P</i>
<i>n</i>	30	30		
Gender			0.30	0.584
Male	19	21		
Female	11	9		
Age (yr)	66.0 \pm 8.0	70.9 \pm 9.4	1.781	0.083
Length (cm)	3-10	2-12		
Average (cm)	5.5 \pm 1.8	6.2 \pm 3.1	0.962	0.342
Location			0.018	0.985
Upper-thoracic	4	6		
Middle-thoracic	23	19		
Lower-thoracic	3	5		
Stage			1.920	0.089
I	0	2		
II	17	12		
III	13	16		
WBC ($\times 10^9/L$)	6.4 \pm 1.9	6.1 \pm 2.0	0.443	0.660
HGB (g/L)	138.4 \pm 14.4	131.4 \pm 17.1	1.411	0.166

(MR) was definite improvement in the barium esophagogram but with $< 50\%$ regression, with a large residual ulcer crater and/or narrowing of the esophageal lumen, regardless of the residual state of the mass shadow. No change (NC) was no improvement in the X-ray findings, with a deep and large residual ulcer or complete obstruction of the esophageal lumen, regardless of the residual state of the mass shadow^[10]. Acute radiation toxicity was evaluated by the Radiation Therapy Oncology Group (RTOG) toxicity criteria.

Statistical analysis

Statistical analysis was done by SPSS (Version 10.0). *t*-test, Chi-square test, or Wilcoxon-*W* test were used to compare the patients' characteristics, tumor response, and normal tissue toxicity to RT of both groups.

RESULTS

Early tumor response

One patient in the CAIR group interrupted RT because of multi-metastasis and another patient in CR group died from cardiac muscle infarction in the schedule. Within three months after RT, the patients that completed the schedule planned were evaluated by criteria as described above. In the two groups, efficiency rate (CR plus PR) was 82.8% (24/29) and 58.6% (17/29), respectively and, accordingly, the inefficiency rate (MR plus NC) was 17.2% (5/29) and 41.4% (12/29), respectively. The difference in tumor response to RT was statistically significant, the efficiency rate in the CAIR group was higher than the CR group ($P = 0.047$). The immediate response of the two groups of patients to RT are listed in Table 2.

Acute radiation reactions

Table 3 shows the acute radiation reactions during the treatment course and up to three months after RT. We found that acute radiation esophagitis and tracheitis in both groups was mainly grade I-II and the difference between the two groups was not statistically significant. No patient received treatment resulting in intolerable acute

Table 2 Tumor response to RT *n* (%)

Group	CR	PR	MR	NC	χ^2	<i>P</i>
CAIR	8 (27.6)	16 (55.2)	4 (13.8)	1 (3.4)	4.08	0.047
CR	6 (20.7)	11 (37.9)	12 (41.4)	0		

radiation reactions in either group.

Impact on blood cell and hemoglobin level

In the CAIR group, the total number of white cells declined below normal level in 5 patients within two weeks after beginning RT. In three of them, white cell counts normalized by medical intervention. In three patients of the CR group, total number of white cell declined below normal level. In both groups, there were two whose patients, total number of white cells did not increase right up to the end of RT. Furthermore, all patient's hemoglobin level had no statistically significant change during the treatment course.

DISCUSSION

Esophageal carcinoma is one of most common malignant diseases in China. The prognosis for patients with esophageal carcinoma is extremely poor. The five years survival rate is 5%-10% for CR alone. The poor prognosis is the result of both local treatment failure, seen in up to 80% of cases, and early disease dissemination^[3,10]. Thus, for esophageal carcinoma, local control is at present the most important factor in prolonging survival. Accelerated repopulation of tumor cells during conventionally fractionated radiotherapy is a proposed reason of failed local control in head-and-neck tumors. In the clinical setting, one goal of treatment is to limit the extent of tumor cell regeneration that occurs during a course of fractionated RT. There is radiobiological rationale and convincing evidence from a number of clinical studies that a therapeutic gain may be achieved, at least for head and neck cancers, when conventional fractionation is modified by reduction in size of dose per fraction with the increase in total dose, reduction of overall treatment time, or both^[9,11]. Rapid repopulation of tumor clonogens is able to compensate about 0.6 Gy/d^[5], beginning after a lag period, which on average, in head and neck tumors is about 3-4 wk from the inception of therapy^[12]. Thus, shortening overall treatment time should limit the extent of accelerated tumor repopulation, and therefore one may expect an increase in the probability of tumor control for given total dose. Since treatment time is thought to have little or no influence on the response of late reacting normal tissue, a reduction in overall treatment time would not be expected to affect the incidence and severity of late normal tissue injury (provided the size of dose per fraction is not increased and the interfraction interval is sufficient for repair to be completed). These concepts became a basic rationale for the development of various altered fractionation strategies as an alternative to conventional fractionation^[13,14]. Simultaneously with reduced treatment time schedules, multiple fraction per day regimens have been used^[15-17]. They allow a higher

Table 3 Grade of acute reaction (RTOG) of esophagus and bronchus according to fractionation regimen *n* (%)

Groups	I	II	III	IV	<i>Z</i>	<i>P</i>
Esophagitis					0.855	0.376
CAIR	6 (20.7)	19 (65.5)	4 (13.8)	0		
CR	11 (37.9)	13 (44.8)	5 (17.2)	0		
Tracheitis					0.051	0.959
CAIR	14 (48.3)	10 (34.5)	5 (17.2)	0		
CR	13 (44.8)	13 (44.8)	3 (10.4)	0		

total dose to be given within the tolerance of late responding normal tissues.

One modality currently in use to achieve this goal is the concomitant boost schedule designed by Maciejewski B *et al*^[18] on carcinoma of the head-and-neck. Their data indicated when dose per fraction of 2.0 Gy given once-a-day at 24 h intervals, an analysis of severe mucosal reactions shows significant difference between CAIR group and CR group. Developed severe mucositis was 48% of patients and 5%, respectively. Their conclusion was that the accelerated treatment, using daily fractions of 2.0 Gy, 7 d per week, gives unacceptable toxicity. When dose per fraction was lowered from 2.0 Gy to 1.8 Gy, the overall rate of acute mucosal reactions decreased to 10% as reported by Skladowski K *et al*^[9]. Both the 3 years local control rate and the 3 years survival rate was improved. The 3-year local tumor control was 82% in the CAIR group and 37% in the CR group, and 3 years overall survival was 78% and 32%, respectively.

In our trial, dose per fraction was 2.0 Gy in both groups. The data showed that acute radiation esophagitis and tracheitis in both groups was mainly grade I-II, and the difference between the two groups was not statistically significant. No patient received treatment resulting in acute radiation reactions that could not be tolerated in either group. The immediate response of two group patients to RT was statistically significant. The efficiency rate (CR plus PR) was 82.8% (24/29) and 58.6% (17/29), respectively, the CAIR group was significantly better than the CR group (*P* = 0.047). The overall treatment time has been shortened by two weeks, as given in the result section.

The present trial demonstrates that seven-day-per-week continuous accelerated irradiation provides significant therapeutic benefit for patients with esophageal carcinoma with regard to both response and toxicity to RT. Fractions of 2.0 Gy could keep acute radiation esophagitis and tracheitis on a tolerable level (different from Maciejewski B). The results of our trial suggest that local control in patients with esophageal carcinoma might be improved by CAIR compared to CR methods, when using dose escalation by continuous accelerated irradiation (with sufficiently long interfraction intervals) and a shorter overall treatment time.

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