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Short Communication

Modulation of Toxicity Following External Beam Irradiation Preceded by High-dose Rate Brachytherapy in Inoperable Oesophageal Cancer

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To induce fast relief of dysphagia in inoperable oesophageal cancer, we applied high-dose rate (HDR) intraluminal irradiation followed by external irradiation (EBRT) in a phase II study. 15 patients (group A: n = 15; 10 men, 5 women; median age 66 years) were treated with 10 Gy HDR brachytherapy plus 40 Gy EBRT (15 fractions of 2.67 Gy). Severe side-effects were encountered in 60% of patients: 3 late ulceration, 2 pending fistula, 2 fistula and 2 patients with fatal haemorrhage after an interval of 6 months. Overall response was excellent: 9 complete remissions (60%) and 6 partial responses (40%). Because of the high toxicity rate, in a subsequent study (group B: n = 30; 23 men, 7 women; median age 66 years) the EBRT scheme was changed using smaller fractions (2.0 Gy) to reach the same total dose of 40 Gy. The complication rate (17%) was significantly reduced, while the overall response remained excellent (83%): 17 complete and 8 partial responses. The impressive change in complication rate of HDR brachytherapy and EBRT stresses the impact of the fraction per dose and illustrates the small therapeutic margins.

Key words: intraluminal brachytherapy, oesophageal carcinoma, radiation injury, fistula, side-effects, dose fractionation

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INTRODUCTION

Carcinoma of the oesophagus is a relatively uncommon tumour. At the time of diagnosis, the majority of patients has advanced disease, not amenable for surgery [1]. Dysphagia and subsequently weight loss are the main problems for which adequate palliation may be achieved by insertion of an endoprosthesis [2] in patients with a poor condition, or by radiotherapy to achieve more prolonged palliation [3, 4]. Approximately 10 years ago, the technique of intraluminal irradiation was introduced [5]. Various methods have been described, using different radiation sources, for example, ^{137}Caesium [5, 6] and ^{192}Iridium [7, 8] with either low (<2 Gy/h), medium (2–12 Gy/h) or high-dose rate (HDR) (>12 Gy/h) technique [9] and various combinations, for example, with laser [7] or with external beam radiotherapy (EBRT) ([6, 10], ICRU report 38). We report on the toxicity of EBRT preceded by HDR brachytherapy.

MATERIALS AND METHODS

Between June 1990 and December 1992, 45 consecutive patients with inoperable oesophageal cancer entered a prospective study at the Netherlands Cancer Institute. Staging procedures consisted of physical examination, laboratory tests (haematology and blood chemistry), chest X-ray, a barium swallow, endoscopy, and CT scan of the mediastinum and liver. The extent of disease was classified according to the UICC staging system using the TNM classification (1985).

Patients with deep ulceration leading to a high risk of fistula formation were excluded. Invasion of the trachea at exploration was not a contraindication unless there was extension into the musoca of the trachea at bronchoscopy.

Initially, patients (n = 15) were treated with the combination of 10 Gy HDR brachytherapy 2 weeks later followed by 40 Gy EBRT in 15 fractions of 2.67 Gy (scheme A). Because of unacceptable toxicity, the dose per fraction of the

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EBRT was reduced to 2.0 Gy (scheme B) in subsequent patients (n = 30).

Brachytherapy was performed using a high-dose rate afterloader (Nucletron) with a ^{192}Iridium radiation source. The outer diameter of the catheter was 6 mm. The source was positioned along the macroscopic tumour length plus 1 cm at the lower and upper level. A dose of 10 Gy was optimised at 1 cm from the source axis.

EBRT was delivered by a linear accelerator (6 or 8 MV). The dose was specified according to ICRU report number 38. Opposed antero-posterior and postero-anterior fields were used. The elective fields included a 5 cm margin from the macroscopic tumour length and 2 cm margins from the width.

Evaluation of symptoms and signs was performed at regular intervals of 6 to 8 weeks. Endoscopy was the evaluation parameter of choice. Responses as well as toxicity were assessed according to WHO criteria.

For comparison of the initial data on patients in both treatment groups as well as treatment outcome, Fisher's Exact test, Mann–Whitney test and the log-rank test were used where applicable.

Survival time was calculated from the start of radiotherapy to the time of death or the last follow-up. Follow-up was until death. Median follow-up of patients alive (n = 5) at the time of the analysis of the present study was 28 months (range 15–36 months).

RESULTS

The pretreatment characteristics (Table 1) were similar in both treatment groups.

Toxicity following scheme A (Table 2) was present in 10 patients (67%): 1 acute, but mild oesophagitis; 9 (60%) severe and late in nature, with a median interval of 6 months (range 2–8 months) from the start of treatment. Eating and drinking were painful in 9 cases with the need for analgetics on a daily basis. Although pain was already present before irradiation in 6 of these patients, pain became more severe over time.

With scheme B, toxicity was quite different (Table 2): more, often (27%) acute side-effects were seen (versus 7% in treatment A), but symptoms were mild and transient, with the need for analgetics in only 3 patients. Severe late radiation damage was significantly less frequent with treatment B compared with treatment A with 17 versus 60% (P = 0.0057). As expected, the need for analgetics was diminished, although not significantly (P = 0.11). Tumour response (Table 2) was excellent for both treatment schemes. Following scheme A, the overall response rate was 100%; improvement of the dysphagia score was present in 13 patients (87%); median

Table 1. Pretreatment characteristics of patients with oesophageal cancer

	Treatment A* (n = 15)	Treatment B† (n = 30)
Male	10	23
Female	5	7
Median age (years) (range)	66 (48–83)	66 (49–90)
Pathology		
Squamous cell carcinoma	7	13
Adenocarcinoma	8	17
Tumour length (cm)		
Median (range)	6 (2–13)	7 (4–17)
Localisation		
Upper	1	1
Middle	6	9
Lower	8	20
Stage I	0	0
Stage II	6	11
Stage III	2	8
Stage IV	7	11
Explorative laparotomy	6	13
Dysphagia		
Almost normal	1	5
Soft food	2	4
Mashed food	5	11
Fluids	7	10
Weight loss (kg)		
Present weight	14	24
Median (range)	9 (1–25)	7 (1–22)
Pain		
At eating	4	2
At obstruction	1	7
Continuous	1	2

*10 Gy HDR intraluminal irradiation and 40 Gy EBRT in 3 weeks (fraction dose 2.67 Gy).
†Similar total dose, but EBRT fraction dose of 2.0 Gy.

Table 2. Treatment results according to different radiation schemes in patients with oesophageal cancer

	Treatment A* (n = 15)		Treatment B† (n = 30)		P-value
No side-effects	3		13		
Acute					
Mild oesophagitis	1		8		0.24
Late					
Ulceration	3		3		
Necrosis, impending fistula	2		0		
Fistula	2		2		0.0057
Fatal haemorrhage	2		0		
Total	9 = 60%		5 = 17%		
Pain					
Before treatment	6		11		
After treatment	9		9		
Analgetics					
Paracetamol	0		1		
PC20	3		4		
PC40	3		2		0.11
Morphine	3		2		
Total	9 = 60%		9 = 30%		
Objective response					
Complete remission	9		17		
Partial response	6	RR = 100%	8	RR = 83%	
No change	0		5		
Dysphagia					
Almost normal	7		15		
Soft food	3		9		
Mashed food	4		2		
Fluids	1		4		
Actuarial survival					
Median in months (range)	10 (4–50)		10 (3–36)		
1 year survival	33%		36%		
2 year survival	13%		20%		

*10 Gy HDR il + 40 Gy/3 weeks EBRT. †10 Gy HDR il + 40 Gy/4 weeks EBRT. PC = paracetamol 500 mg plus codeine either 20 or 40 mg. RR, response rate.

survival was 10 months. Following scheme B, data were similar in terms of local response rate (83%) and median survival (10 months).

DISCUSSION

For inoperable oesophageal cancer, radiotherapy is widely applied with durable palliative intent. However, the prognosis is poor and overall survival time relatively short with a median survival of 10–11 months [6, 10]. In recent years, the technique of intraluminal irradiation has become available in many centres and is mainly used to give a boost directly on the tumour following EBRT [8, 10, 12, 13], aiming at improved local control compared with EBRT alone [9]. However, brachytherapy and especially the use of a high-dose rate source may provide a fast and simple procedure to induce rapid tumour regression and relief of dysphagia when applied before EBRT [6, 7]. The selection of the brachytherapy dose of 10 Gy HDR was based on work of Flores and colleagues [6] and Hishikawa and colleagues [9, 10]. Flores and colleagues used a dose of 15 Gy medium-dose rate (MDR). The difference in radiobiological effect between HDR and low-dose rate (LDR) radiotherapy is well known. The difference between HDR and MDR radiotherapy, however, is less well established. When we started to treat patients with treatment schedule A, correction for the possible difference between HDR and MDR seemed safe. An important difference between Hishikawa's series and ours is the timing of the brachytherapy. In the present study, brachytherapy preceded EBRT. Therefore, we expected that the very high doses at the surface of the application would damage macroscopic tumour and not the healthy tissue. There is limited information in the literature concerning side-effects and complications of irradiation in oesophageal cancer. The few papers dealing with radiation ulcers or fistulas arise from series in China [11] and Japan [14, 15]. The aetiology of a radiation ulcer is complex, but a high total dose and large fractional dose might promote radiation ulcers. In the present study, treatment scheme A was discontinued due to unacceptable toxicity. Explanations for our experience with scheme A might be patient selection, total dose and dose per fraction of EBRT, or the brachytherapy dose. Selection of patients in non-randomised studies is hard to compare in detail with literature data. As in all phase II studies [11, 14], deep ulceration before treatment was considered the only contraindication for radiation therapy. In this study, patients with a tumour located in the middle or distal oesophagus received H_2-blockers or proton pump inhibitors routinely to reduce trauma by reflux of gastric acid. After the introduction of a protective agent in the Japanese series [16], side-effects

were reduced from 50 to 39%. The next step was to consider a change in the radiation scheme. Although the total dose (40 Gy) applied was not extremely high, the dose per fraction (2.67 Gy) might have been too large, as in most series EBRT was applied in fractions not exceeding 2.0 Gy. Therefore, we choose to adjust the EBRT scheme to provide the same dose over more, but in smaller fractions. Subsequently, the incidence of late side-effects was reduced from 60 to 17%. The impact of the relatively high dose of brachytherapy using the HDR technique is difficult to unravel. However, our findings emphasise the small therapeutic margin for the combination of HDR brachytherapy and EBRT.

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