British Journal of Cancer (1996) 74, 1452-1457

High dose rate brachytherapy before external beam irradiation in inoperable oesophageal cancer

BG Taal[1], BMP Aleman[2], CCE Koning[2] and H Boot[1]

Departments of [1]Gastroenterology and [2]Radiotherapy, Netherlands Cancer Institute/Antoni van Leeuwenhoekhuis, Amsterdam, The Netherlands.

Summary To induce fast relief of dysphagia in patients with oesophageal cancer high dose rate (HDR) brachytherapy was applied before external radiotherapy in a prospective study. Seventy-four patients with inoperable oesophageal cancer (36 squamous cell, 38 adenocarcinoma) were treated with a combination of 10 Gy HDR brachytherapy, followed by 40 Gy in 4 weeks external beam radiotherapy (EBRT), starting 2 weeks later. Tumour response, as measured by endoscopy and/or barium swallow, revealed complete remission in 21 and partial response in 38 patients (overall response rate 80%). Improvement of dysphagia was induced by brachytherapy within a few days in 39%, and achieved at the end of treatment in 70% of patients. Further weight loss was prevented in 39 of the 59 patients who presented with weight loss. Pain at presentation improved in 12 out of 25 patients. Median survival was 9 months. No differences in either response rate or survival were found in squamous cell or adenocarcinoma. Side-effects were either acute with minimal discomfort in 32 (42%) or late with painful ulceration in five patients (7%), occurring after a median of 4 months. A fistula developed in six patients, all with concurrent tumour. In conclusion, brachytherapy before EBRT was a safe and effective procedure to induce rapid relief of dysphagia, especially when combined with EBRT.

Keywords: oesophageal cancer; brachytherapy; radiotherapy

The prognosis of oesophageal cancer is usually dismal. Surgery is potentially curative in only a small subset of patients (Altorki and Skinner, 1990). Oesophageal resection is considered major surgery, which includes substantial morbidity and mortality. Although post-operative mortality has decreased over the last years and is acceptably low (5%) in some centres, resection as a palliative measure is not widely accepted in clinical practice. In the case of unresectable oesophageal cancer or advanced locoregional disease, radical radiotherapy may offer adequate palliation (Beatty *et al.*, 1979), although overall prognosis is poor and progression may be apparent even during irradiation in up to 20% of patients (Wara *et al.*, 1976). Since the review of the literature (1954-1979) on the role of radiotherapy by Earlam and Cunho-Melo (1980), radiation techniques have changed, especially after brachytherapy was in favour again when remote control techniques became available, as described by Rowland and Pagliero (1985); followed by others (Petrovich *et al.*, 1991; Smalley *et al.*, 1994). In most studies (Caspers *et al.*, 1993; Flores *et al.*, 1989; Gaspar, 1994; Hishikawa *et al.*, 1991; Hyden *et al.*, 1988; Sur *et al.*, 1992), intracavitary irradiation has been used as a booster following external radiotherapy, which has the advantage of delivering a high dose to a small tumour volume.

As dysphagia is the main symptom in oesophageal cancer leading to weight loss and deterioration of the general condition, we applied brachytherapy before EBRT to induce rapid tumour reduction and subsequent relief of dysphagia. Aiming at optimal tumour regression and improved quality of life, at the cost of minimal side-effects, we based our regimen on the two largest series in the literature: that of Flores *et al.* (1989), who combined a short course of EBRT (40 Gy over 3 weeks) with medium dose rate brachytherapy (15 Gy), and the wide experience of Hishikawa *et al.* (1991) using high dose rate (2 × 6 Gy) in addition to EBRT (60 Gy over 6 weeks). With regard to dysphagia and the generally short life expectancy, we applied 10 Gy HDR brachytherapy before a short duration radiotherapy scheme, 40 Gy over 3 weeks EBRT. When this appeared to be too toxic in a pilot study, in nine out of 15 patients severe late side-effects, e.g. ulceration, necrosis and fistula formation (Taal *et al.*, 1996), we adapted the regimen by giving the same EBRT dose over 4 weeks. In comparison, in the past, when brachytherapy was not yet available, we applied a 6 week scheme of EBRT only: 40 Gy over 4 weeks plus 20 Gy over 2 weeks as a booster dose to a smaller volume.

In this paper we report on response and side-effects of our new scheme with upfront brachytherapy in a prospective phase II trial.

Materials and methods

Patients

Between February 1991 and September 1994, 74 consecutive patients with advanced inoperable oesophageal cancer entered a prospective study of radiotherapy at the Netherlands Cancer Institute approved by the local medical ethics committee. All patients, including those from the referring hospitals, underwent a diagnostic endoscopy in our institute and were discussed by the gastroenterologist and radiation oncologist. The diagnosis was based on endoscopic biopsies. Routine staging procedures consisted of physical examination, laboratory tests (haematology and blood chemistry), chest radiograph, a barium swallow, endoscopy, computerised tomography (CT) scan of the mediastinum and liver or ultrasonography of the liver. In addition to this clinical staging, information available from explorative laparotomy was included in 30 patients. The extent of disease was classified according to the 1987 UICC staging system using the TNM classification (Table I). Because this staging system is especially developed for surgically treated patients, additionally other tumour characteristics are mentioned. Still, there is some 'understaging' in patients who did not undergo surgery.

Eligibility criteria included: adeno- or squamous cell carcinoma of the oesophagus or cardiac junction when the main part of the tumour was localised in the oesophagus, inoperable tumours owing to infiltration into surrounding

Correspondence: BG Taal, Nederlands Kanker Instituut/Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Received 15 January 1996; revised 21 May 1996; accepted 24 May 1996

Table I TNM classification and UICC stages in oesophagal cancer

T	Primary tumour		
T_1	Tumour invades lamina propria or submucosa		
T_2	Tumour invades muscularis propria		
T_3	Tumour invades adventitia		
T_4	Tumour invades adjacent structures		
N	Regional lymph nodes		
N_0	No regional lymph nodes		
N_1	Regional lymph node metastases		
M_1	Lymph node metastases at the coeliac axis		
M	Distant metastases		
M_0	No metastases		
M_1	Haematogenous metastases		
UICC staging			
Stage			
I	T_1	N_0	M_0
IIA	T_2	N_0	M_0
	T_3	N_0	M_0
IIB	T_1	N_1	M_0
	T_2	N_1	M_0
III	T_3	N_1	M_0
	T_4	AnyN	M_0
IV	AnyT	AnyN	M_1

tissues or distant lymph node metastases (e.g. at the coeliac axis), or patients considered unfit for surgery; WHO performance $\leqslant 2$; no age limits; informed consent was obtained in all patients. Excluded were patients with deep ulceration or necrosis (less than 5% of all patients), and patients with extension into the mucosa of the trachea at bronchoscopy, because the risk of fistula formation was deemed very high. Infiltration of the trachea at exploration was not a contraindication.

Patients with a tumour located in the middle or lower oesophagus were advised to take an H_2-blocker or proton pump inhibitor to reduce gastric acid secretion.

High dose rate brachytherapy (HDR)

The dummy catheter for brachytherapy was introduced by endoscopy after intravenous sedation with 2.5–10 mg midazolam, in some cases combined with 1–2 ml fentanyl plus droperidol (Thalamonal). Administration of oxygen and monitoring by pulse oximeter were applied routinely. The technique was similar to that used by Hishikawa *et al.* (1991), except that the patient remained in the lateral position during the whole procedure to prevent migration of the radiation catheter and aspiration of saliva. The actual procedure started with endoscopic measurement of the tumour length with the patient in the left lateral position; the tip of the endoscope was positioned 1 cm distally to the lower margin of the tumour. Under fluoroscopic control, this position was marked on the skin with a lead wire. A guide wire was introduced and after removal of the endoscope, a calibrated hollow (dummy) catheter with a diameter of 6 mm was inserted up to the level of the lead wire mark on the skin. When the positioning was considered adequate under fluoroscopic control, the guide wire was removed and the dummy catheter fixed with a mouth mask and connected to the Selectron afterloading system for injection of the ^{192}Iridium radiation source into the lumen of the catheter. Subsequently, the ^{192}Iridium core was moved under computer guidance. The target volume consisted of visible tumour length plus 1 cm at the lower and upper level. The delivered dose was calculated using a computerised radiotherapy planning system (NPS). A radiation dose of 10 Gy calculated at 1 cm from the source axis was administered with a high dose rate, which implied that the dose was given in 5–10 min.

External beam radiotherapy (EBRT)

With an interval of 10–14 days after brachytherapy, the external beam irradiation was started. EBRT was delivered by a linear accelerator (6 or 8 MV). The dose was specified according to ICRU Report numbers 29 and 50. Opposed antero-posterior and postero-anterior fields were used. The elective fields included a 5 cm microscopically tumour-free margin in the length of the tumour and 3 cm margins from the width (usually 8 cm wide). A total dose of 40 Gy was given in 20 fractions of 2.0 Gy over 4 weeks.

Evaluation

Evaluation of symptoms and signs such as dysphagia, pain and use of medication, as well as tumour measurements were performed 4–6 weeks after the end of radiotherapy and at regular intervals of 6–8 weeks thereafter. Endoscopy was the evaluation method of choice. In case of patient's refusal, only a barium swallow was performed, combined with a CT scan, when there was suggestion of tumour recurrence. Responses were assessed according to WHO criteria: a complete response (CR) defined as no macroscopic tumour; near complete remission was defined as a residue of only a few mm in diameter detected by endoscopy; a partial remission (PR) occurred when at least 50% tumour reduction was found; no change (NC) was found in case of variation within 50% regression and 25% progression of the tumour; progressive disease was recorded when an increase of at least 25% was present. Biopsies were not routinely taken to document remission. The duration of response was measured from the start of treatment until the first sign of recurrence at endoscopy. For grading of toxicity the WHO recommendations were used. In addition, specific endoscopic patterns were interpreted as acute radiation effect in the case of superficial erosions with a fibrin lining and disappearance of tumour, or chronic radiation ulceration as described by Yang *et al.* (1990), including a demarcation line of ulceration and intact opposite wall of the oesophagus.

Statistics

Survival time was calculated from the start of radiotherapy to the time of death or the last follow-up. Follow-up was until date of death. Median follow-up of patients alive ($n=20$) at the moment of the evaluation of the present study was 6 months (range 2–31 months).

Results

Among the 74 patients, 52 were men (70%) and a minority of 22 (30%) women; median age was 67 years, with a wide range of 49–91 years. Pretreatment characteristics, as summarised in Table II, revealed an almost equal number of squamous cell and adenocarcinomas, which can be expected based on a localisation mostly in the distal (48 or 65%) and middle (23 or 31%) part of the oesophagus. According to the 1987 UICC TNM staging (Table I), the majority of patients (51 or 69%) were in an advanced stage (III or IV). Although 23 patients were in stage II, indicating relatively limited tumour burden, other parameters were considered unfavourable, explaining the preference for radiotherapy instead of surgery, e.g. poor condition ($n=7$), age over 80 years ($n=7$) with moderate condition, a very long (> 10 cm) tumour ($n=5$), or cardiopulmonary contraindication for surgery ($n=4$). Explorative surgery, usually laparotomy, performed in 30 patients, revealed unexpected invasion into the surrounding organs (T4) in ten patients or multiple malignant lymph nodes at the coeliac axis, which are considered as metastatic disease (M1) in 20 patients.

Endoscopic dilatation within 4 weeks before the start of radiotherapy for tumour measurement and palliation of dysphagia was necessary in 24 patients. Treatment results in terms of symptoms and signs (Table III) showed improvement in dysphagia in 52 patients (70%). In approximately half of these patients this symptomatic improvement was present as early as a few days following brachytherapy. The number of

Table II Pretreatment tumour characterisitcs of 74 patients with locally advanced oesophageal cancer

Male + Female	52 + 22
Age, median (range) years	67 (49–91)
Pathology	
Squamous cell carcinoma	36
Adenocarcinoma	38
Length	
Median (range) cm	7 (4–17)
⩽5 cm	16
6–9 cm	51
⩾10 cm	7
Site	
Proximal	3
Middle	23
Distal	48
UICC stage	
I	0
II Length ⩾ 10 cm	5
Poor condition	7
Age > 80 years	7
Cardiopulmonary contraindications	4
III	21
IV	30
Explorative surgery	30
Local invasion	6
Lymph node coeliac axis	18
Both	3
Omental metastases	3
Dilatation needed before radiotherapy	24

Table III Symptoms and signs in 74 patients with locally advanced oesophageal cancer

	Before treatment	*After treatment*
Dysphagia		
Normal	4	25
Almost normal	8	11
Soft food	9	17
Mashed food	18	9
Fluids only	32	9
No fluids	3	2
Dysphagia improvement	–	52
Improvement following brachytherapy	–	29
Pain		
Present	25	22
Better	–	12
Similar	–	10
Worse	–	3
New symptom	–	9
Weight loss		
Present	59	20
⩾10 kg	28	–
Weight gain		
Present	0	5
Hiccup	9	–
Haemorrhage		
Haematemesis	2	5[a]
Melaena	1	1[a]

[a]At the time of recurrent disease: median interval 17 months (range 8–29 months).

Table IV Treatment results in 74 patients with locally advanced oesophageal cancer

	Total	*Squamous*	*Adeno*
Objective response at endoscopy and/or barium swallow			
Complete remission	21	12	9
Near complete	12	2	10
Partial response	26	14	12
No change	10	4	6
Progressive disease	5	4	1
Overall response	59 (80%)	28 (78%)	31 (82%)
Additional treatment of failure			
Dilatation/laser	0		
Endoprosthesis	2		
Local recurrence	40		
Median interval (range)	7 (2–30) months		
Cause of death ($n = 54$)			
From primary tumour	32		
From distant metastases	21		
From intercurrent disease	1		

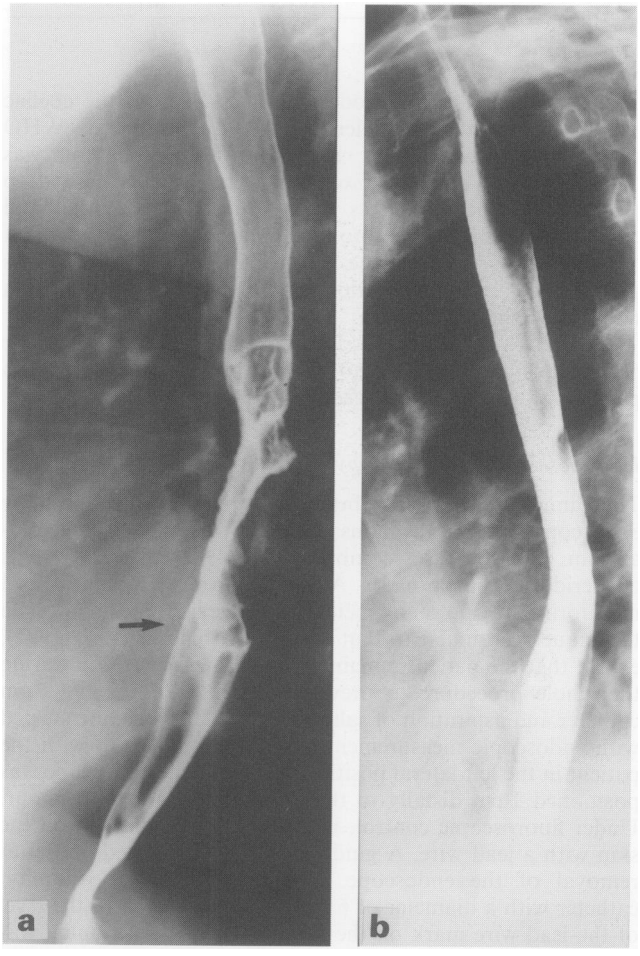

Figure 1 The barium meal in a 74-year-old woman who could take nothing but fluids, leading to weight loss, revealed an obstructing tumour of 6 cm in length (**a**). Following radiotherapy an impressive improvement in dysphagia, owing to tumour reduction at barium meal with some stenosis (**b**); complete remission was confirmed by endoscopy.

patients who could take an almost normal diet increased from 12 (16%) to 36 (49%). In only 15% of the patients dysphagia remained a major problem as they could eat nothing but fluids, compared with 35 patients (47%) before treatment. Along with improvement of dysphagia, no further weight loss occurred in 39 patients, and in five cases even some gain in weight was assessed during the weeks of external radiotherapy.

Retrosternal pain at presentation occurred either at eating ($n = 5$), during obstruction ($n = 8$), or was continuous ($n = 12$). Pain improved in 12 of those 25 patients (48%), but occasionally became more prominent ($n = 3$). In nine other patients pain appeared after treatment. Thus, the overall incidence of pain remained similar.

Although most oesophageal tumours were friable and easily bleeding at endoscopy, haematemesis and melaena were rare conditions at presentation (3 or 4%). Also during follow-up it was seen in only six patients (median interval 17 months), all with tumour recurrence. In four of them it was a terminal and fatal event.

Objective tumour response (Table IV), as evaluated by endoscopy and/or barium swallow, was present in 59 patients (80%): in 21 complete (Figure 1); and 12 near complete with only a small nodule of a few mm at endoscopy (Figure 2); in the other 26 the criteria of partial response with more than 50% tumour reduction were met. In squamous cell carcinoma the overall response was not different from adenocarcinoma (Table IV). As 20 patients were still alive at the time of the analysis, duration of response is not yet fully known. In the 54 patients who had died at the time of analysis, the median duration of response was 6 months (range 2–16 months). Additional treatment directly following radiotherapy, in case of failure, was required in only two cases, in whom a self-expandable stent was inserted. Local recurrence was found in 40 patients during follow-up investigations at regular intervals of 6 weeks according to the trial protocol; this might explain why recurrence was usually found before dysphagia recurred. The need for an endoprosthesis was, therefore, at a later time, median 7–8 months.

At the time of the analysis most patients ($n=54$ or 72%) had died. As shown in the survival curve (Figure 3), the overall median survival was 9 months (range 2–43 months). Subgroup analysis of survival data did not show significant differences for histological type (squamous cell *vs* adenocarcinoma), stage (I + II *vs* III + IV) or explorative surgery (yes *vs* no). In addition, cardia carcinomas did not show a significantly different response, although there were some long-term survivors. As might be expected from the incidence of local recurrence, the cause of death was, despite the presence of distant metastases in several cases, predominantly related to tumour growth at the primary site in 32 out of 54 patients (59%), leading to poor general condition, pneumonia, etc.

No adverse effects related to brachytherapy were found. Side-effects (Table V) were either acute ($n=32$ or 42%) at the end of external radiotherapy, or late with a median interval of 4 months ($n=20$ or 27%). Acute oesophagitis, as observed at endoscopy, was mild and short-lasting (1–2 weeks), leading to some retrosternal burning sensation, but without interfering with eating and without the need for analgesics. Delayed side-effects (> 2 months following radiotherapy) tended to be more severe, among which fistula formation was the most serious. This serious condition of fistula formation, usually diagnosed at radiography, was present in six patients with squamous cell carcinoma in the middle of the

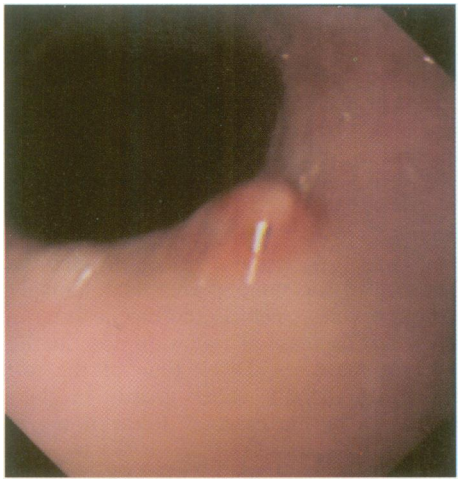

Figure 2 A tiny nodule at endoscopy as the result of impressive tumour reduction in a 66-year-old man with adenocarcinoma of 7 cm; near complete remission after radiotherapy. Progression with the need of an endoprosthesis after 24 months and at 31 months the patient is still alive and well.

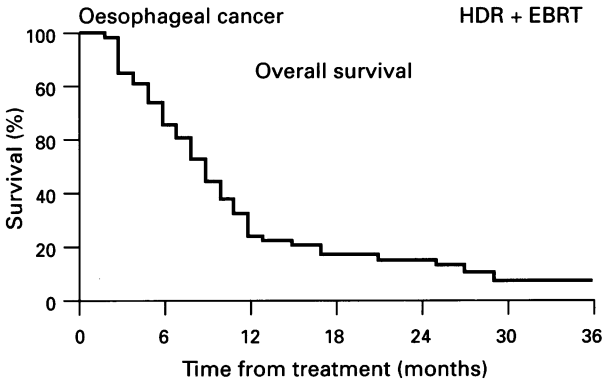

Figure 3 The overall survival in patients with inoperable oesophageal cancer, following an irradiation scheme of HDR brachytherapy and EBRT. Median survival is 9 months.

Table V Side-effects of HDR brachytherapy plus external beam irradiation in 74 patients with oesophageal cancer

None		32
Acute	Mild oesophagitis	19
Delayed[a]	Ulceration	11
	Necrosis	3
	Fistula	6[b]
Haemorrhage	Radiation injury	0
	Recurrent disease	5
	Unknown	1

[a]Median interval 4 months, range 2–11 months. [b]Concurrent tumour, either residue or recurrence, in all six patients.

Table VI Literature data on the effect of EBRT combined with brachytherapy in locally advanced oesophageal cancer

			Radiotherapy			Evaluation	Response		Death from	Survival	
Year	*Author*	n	*Brachy*[a]	*EBRT*	*Brachy*[a]*(Gy)*	*scheme*	*Subjective*	*Objective*	*primary tumour*	*5 year*[b]	*Median*
1988	Hyden	46	–	38–50	1–3×20 MDR	NS	Nearly all	CR 20% PR 76%	35%	0–12%	13 months
1989	Flores	171	[c]	40	15 MDR	Quality of life	90%	NS	NS	19%	11 months
1991	Petrovich	46	–	50	40	Mixed study over 23 years	Good 48%	CR 20% PR 76%	NS	11%	8–13 months
1991	Hishikawa	148	–	60	12 HDR	Interval 1–3 months	NS	LC[d] 64%	20–37%	0–18%	NS
1992	Sur	25	–	35	2×6 HDR	Interval 3 months	90–70%	LC 85–70%	NS	1 year 78%	11
1993	Caspers	35	–	50–60	15–20 LDR	Interval 6 weeks Dilatation + laser in severe obstruction before EBRT	Semi-solid food 80%	CR 29% PR 71%	49%		months
Present series			10 HDR	40	–	Interval 6 weeks to 3 months	70%	CR 28% PR 51%	59%		>8 months

[a]Brachytherapy: LDR, low dose rate (±48 h per application); MDR, median dose rate (2–3 h per application); HDR, high dose rate (5–10 min per application). [b]Presented for the whole group or the variation between limited disease (stages I+II) and extensive disease (stages III+IV). [c]Sometimes brachytherapy before EBRT instead of following EBRT. [d]LC, local control. NS, not specified.

oesophagus, with a median interval of 3 months (range 2–7 months). Although tumour reduction (partial remission) was achieved in five of them, in all six cases tumour residue was clearly present at the end of treatment. Whether fistula formation was merely related to radiation injury or caused by tumour residue or both remained uncertain. Ulceration or even necrosis following irradiation, was found in 11 and 3 patients respectively. Only five of these patients (7%) needed analgesics: four suffered from pain before radiation therapy, which unfortunately increased during follow-up, although partial remission was observed at endoscopy.

Discussion

Despite the large-scale availability of endoscopic diagnostic techniques and improvement in surgical, as well as endoscopic, treatment options, the prognosis of oesophageal cancer is still poor, because patients are often malnourished and presenting with locally advanced or disseminated disease. In addition, many patients are of advanced age, and so have limited ability to resist complications of aggressive surgery. Hence, adequate long-term palliation by rapid relief of dysphagia is the main goal of treatment. In patients with metastatic disease or those in very poor condition this might most easily be achieved by endoscopic treatment, such as dilatation, laser coagulation, or the insertion of an endoprosthesis (Bown, 1991). The new generation of coated self-expandable stents are especially indicated in case of oesophago-bronchial fistula (Taal *et al.*, 1995*a*). However, for patients with locally advanced disease, but still in fair condition, it is widely accepted to apply radiotherapy to achieve adequate palliation. Various schemes of irradiation are being used. Regimens to achieve long-term palliation or even cure are usually referred to as radical radiotherapy in the literature, and consist of doses of 50–60 Gy delivered in 5–6 weeks. Nevertheless, figures of 5 year survival are only 6% as mentioned in the well-known review of Earlam and Cunho-Melo (1980). Even in several other series, up to 85% of patients still die from persistent or recurrent primary tumour (Beatty *et al.*, 1979; Smalley *et al.*, 1994). Therefore, improvement in results is greatly needed. Intraluminal radiotherapy (brachytherapy) is not new, but recent technical advances allowing HDR brachytherapy may offer several advantages over the conventional technique of external irradiation alone: better local control, reduction of treatment time and, when given before external radiotherapy, rapid improvement of dysphagia.

Several studies (Hyden *et al.*, 1988; Petrovich *et al.*, 1991; Sur *et al.*, 1992) claimed better local control by adding brachytherapy to external beam radiotherapy. In the only prospective trial available (Sur *et al.*, 1992), a booster dose applied by brachytherapy compared favourably with the booster given by external application. It should be noted that the numbers (25 patients per arm) are very small. In the other reports (Hyden *et al.*, 1988; Petrovich *et al.*, 1991), being retrospective studies over many years, the beneficial effect of brachytherapy may be attributable to patient selection and changes in staging procedures over the years. Staging according to the 1987 UICC classification is very difficult in groups of patients who are irradiated, because information otherwise acquired by surgery, is not available. CT scan of the mediastinum and abdomen, and even endoscopic ultrasonography (EUS) lack accuracy for determining exact information on depth of infiltration and lymph node metastases (Smalley *et al.*, 1994; Sur *et al.*, 1992). In the present series, there might be some understaging, especially when patients were not particularly fit, and additional staging procedures were limited. This might explain why, in patients in stage II, often unfavourable aspects were found, such as a long tumour traject and a poor condition, pointing to a more advanced stage. However, all reported radiotherapy series included stage II–IV. In our series only patients with locally deep ulceration or necrosis were excluded, which was seen in approximately 5% of all patients referred for radiotherapy, and haematogenous metastases. Whether brachytherapy resulted in better local control compared with conventional schemes remains uncertain, and was not the objective of our study. Anyway, local effect was excellent with impressive tumour reduction in 80% and improvement in 70% of patients. On the other hand, 59% of patients still died of the primary site. Median survival was similar to that in the literature (Flores *et al.*, 1989; Hishikawa *et al.*, 1991).

Most studies (Table VI) have applied brachytherapy as a booster following external radiotherapy. The main problem in oesophageal cancer, however, is dysphagia, leading to weight loss and eventually malnutrition and poor condition. To induce rapid tumour reduction and, hence, relief of dysphagia, another potential advantage of brachytherapy, this technique was applied before external radiotherapy in the present study in contrast to most series in the literature (Table VI). Results lived up to expectations: improvement of dysphagia occurred within a few days in 39% of patients, and at the end of the combined treatment in 70% of patients. Further weight loss was prevented and even some weight gain occurred during the 4 weeks of external radiotherapy. Side-effects were acceptable. Several patients suffering from pain before treatment improved, but in others pain appeared as a result of radiation-induced ulceration. Overall, the incidence of pain before and after radiotherapy was not different. Chronic ulceration with the need for analgesics occurred in 7% of patients. Mucosal protection with sucralphate offered little benefit to our patients with radiation ulcers, ascribed to short duration of mucosal coating (Taal *et al.*, 1995*b*). Development of a fistula occurred only in the presence of residual tumour and the contribution of radiotherapy to the occurrence of a broncho-oesophageal fistula was difficult to judge, as this is also a well-known event in the natural course of oesophageal cancer. Haemorrhage was a serious complication and proved fatal in four of the six patients. However, this was a terminal event caused by tumour recurrence and not treatment related.

A third major advantage of brachytherapy is a reduction of treatment time. A large dose of irradiation can be delivered directly to the tumour area with limited injury to the surrounding tissues, such as the mediastinum and lung, because of a steep decrease of radiation dose as the distance from the source increases. Dwell time of the intraluminal catheter for brachytherapy varies greatly in the literature from several days in the case of a low dose rate source (Caspers *et al.*, 1993; Hyden *et al.*, 1988) to several hours with a medium dose rate applicator (Flores *et al.*, 1989). Application of brachytherapy with the high dose rate source (Hishikawa *et al.*, 1991; Sur *et al.*, 1992), as applied in the present study, takes only 5–10 min, enabling the procedure to be performed as an outpatient treatment. Another reduction in treatment time can be achieved by a decrease in total dose of external irradiation, when combined with brachytherapy. For comparison, our previous treatment schedule included 6 weeks of external irradiation only, with a total dose of 60 Gy delivered in 30 fractions or 30 hospital visits, similar to the radical radiotherapy schemes reported in the literature. In the new scheme one session of brachytherapy was combined with 4 weeks of external irradiation (20 fractions), thus a reduction of 2 weeks (ten visits). From the patients' point of view, upfront brachytherapy was a simple and safe procedure: improvement of dysphagia occurred within a few days, leading to improved quality of life and enabling the patients to undergo external radiotherapy without the need of dilatation procedures. A single application of brachytherapy may be useful too in the palliation of dysphagia, as reported in a large series by Brewster *et al.* (1995). However, responses are usually of shorter duration (4 months) compared with the combined irradiation schemes (8–9 months). Therefore, in our institute brachytherapy alone is especially recommended in patients with a short life expectancy.

In conclusion, upfront HDR brachytherapy resulted in

rapid improvement of dysphagia and, when combined with a condensed external radiation scheme, adequate long-term palliation was achieved in both squamous and adenocarcinoma alike. Although local response was excellent and side-effects acceptable, eventually patients suffered from local recurrent disease, which was rapidly fatal in 59%. Thus, there is still a major need for improvement of long-term results, which might be achieved by a higher dose of external radiotherapy, as used by Hishikawa *et al.* (1991), or by combining radiotherapy with multiagent full dose chemotherapy. A review of studies (Rich and Ajaui, 1994) reporting the results of combined modality, showed a modest benefit compared with radiotherapy alone, e.g. an increase in median survival from 8 to 12 months at the cost of increased toxicity (Herskovic *et al.*, 1992) or some long-term survivors (Coia *et al.*, 1991). Another option, using a low-dose chemotherapy scheme as radiosensitiser, might be of benefit. Such an approach has been shown to improve local control, and eventually survival, in non-small-cell lung cancer (Schaake-Koning *et al.*, 1992). Combinations of radiotherapy schemes, including brachytherapy to induce rapid relief of dysphagia, with chemotherapy to achieve long-term survival, will be the subject of a future trial in the Netherlands.

Acknowledgements
The authors wish to thank AAM Hart for statistical procedures and Mrs E Peetam-Brugman for accurately editing the tables.

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