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The Management of Radiation-associated Oesophageal Carcinoma: a Report of 16 Cases

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16 patients, presenting with squamous cell carcinoma in previously irradiated sections of the oesophagus, are described. Oesophagectomy could be performed in 2 patients, resulting in long-term disease-free survival (38 and 60 months after diagnosis). 14 patients were treated with palliative radiotherapy (external beam or intraluminal), oesophageal stenting, bougienage or chemotherapy. Although most patients previously received curative dosages of mediastinal irradiation, additional full courses of high-dose radiotherapy could be given on five occasions; no major complications were encountered and adequate palliation for up to 10 months was achieved. Similar results were observed after oesophageal stenting and/or bougienage. Relief of dysphagia following intraluminal radiotherapy or chemotherapy was only minimal (2 months or less). Median survival in the palliative treatment group was 6.5 months (range 2–27 months), which is in keeping with results observed in non-radiation-associated oesophageal carcinoma. We concluded that, in selected cases, both surgery and radiotherapy offer good prospects for patients with radiation-associated oesophageal cancer.
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INTRODUCTION

RADIATION-ASSOCIATED oesophageal carcinoma is defined as malignancy developing in a previously irradiated section of the oesophagus. Additional, but non-essential features are a long latent interval and evidence of radiation injury in surrounding tissue [1, 2]. This condition is rare. Since 1959, only 37 patients have been described in the literature [1–20] (Table 1).

In the present study, 16 additional cases from The Netherlands Cancer Institute are discussed, the largest series from a single hospital published thus far.

Apart from describing the clinical picture of radiation-associated oesophageal carcinoma, we summarise our experience in treating this condition. This appears to be of particular interest, as earlier publications contain very little information on this subject whereas even less is known about the prognosis of this type of malignancy.

PATIENTS AND METHODS

Scanning of tumour registry data and endoscopy reports revealed 16 patients, treated for radiation-associated oesophageal carcinoma in The Netherlands Cancer Institute between 1977 and 1991. We conducted a retrospective study which involved a review of their medical records, radiotherapy data and diagnostic X-rays.

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RESULTS

Of the 16 patients studied, 7 (44%) were men and 9 (56%) were women. The median age on diagnosis was 56 years (range: 32–83 years). Oesophageal carcinoma was demonstrated 2–63 years (median: 8.5 years) after therapeutic irradiation for malignancy (13 cases) or benign disorders (3 cases) (Table 2).

Most patients presented with a 1–6 month history of progressive dysphagia, occasionally accompanied by weight loss or fatigue.

Chronic intermittent dysphagia of 1–3 years duration was mentioned in 5 cases (numbers 2, 5, 6, 7, 9, Table 2); only one of them was examined endoscopically on an earlier occasion; at that time, biopsies were positive for chronic inflammation (case 9, Table 2). 1 patient did not suffer from dysphagia (case 2, Table 2); instead, she indicated intermittent retrosternal pain which had been present ever since irradiation of the internal mammary chain for inner quadrant breast carcinoma 2 years earlier. Endoscopy, performed after sudden deterioration of her complaints, quite surprisingly revealed squamous cell carcinoma of the oesophagus.

Endoscopic biopsies in the other 15 cases were also compatible with squamous cell carcinoma most of which occurred in the proximal third of the oesophagus (12/16 = 75%); tumour length, known in 14 patients, was assessed endoscopically in 12

Table 1. Cases of radiation-associated oesophageal carcinoma reported in the world literature

Ref.	Initial lesion	Initial RT dose (Gy)	Interval (years)	RAOC at age (years)	RAOC histology
3	Breast carcinoma	40	16	79	Squamous cell carcinoma
	Breast carcinoma	49	34	76	Squamous cell carcinoma
	Breast carcinoma	40	12	72	Squamous cell carcinoma
	Breast carcinoma	40	13	69	Squamous cell carcinoma
	Breast carcinoma	40	8	56	Squamous cell carcinoma
	Breast carcinoma	40	7	70	Small cell carcinoma
4	Breast carcinoma	50	3	47	*
	Breast carcinoma	*	5	85	*
	Breast carcinoma	*	14	61	*
	Breast carcinoma	*	6	73	*
	Breast carcinoma	*	8	66	*
	Breast carcinoma	100	9	48	Squamous cell carcinoma
5	Breast carcinoma	18.6	16	74	Squamous cell carcinoma
	Breast carcinoma	41.8	12	71	Squamous cell carcinoma
6	Larynx carcinoma	49	8	59	Fibrosarcoma
7	Larynx carcinoma	*	26	57	*
8	Larynx carcinoma	*	17	86	*
	Larynx carcinoma	45	10	73	*
9	Hodgkin's disease	38	11	30	Squamous cell carcinoma
10	Hodgkin's disease	40	10	52	Squamous cell carcinoma
11	Hodgkin's disease	39	18	67	Squamous cell carcinoma
2	Embryonal carcinoma testis	60	12	33	Squamous cell carcinoma
	Terato-carcinoma testis	40	28	63	Squamous cell carcinoma
12	E.D. mass Th. spine†	*	10	60	*
13	Lung carcinoma	50	11	59	Squamous cell carcinoma
1	Lymphosarcoma	25.5	10	60	Squamous cell carcinoma
14	Thyrotoxicosis	21	17	34	*
15	Thyrotoxicosis	*	37	79	Squamous cell carcinoma
16	Thyrotoxicosis	*	45	76	Squamous cell carcinoma
17	Thyrotoxicosis	32	40	71	Squamous cell carcinoma
13	Thyrotoxicosis	32	30	71	Squamous cell carcinoma
18	Tuberculous adenitis	*	43	61	Squamous cell carcinoma
19	Tuberculous adenitis	*	31	51	Squamous cell carcinoma
20	'Swollen glands neck'	*	27	51	Adeno carcinoma
14	Goiter	*	52	66	*
	Goiter	40	50	66	*
11	Myasthenia gravis	*	24	56	Squamous cell carcinoma

RAOC: radiation-associated oesophageal carcinoma; RT: radiotherapy (dose applied for initial lesion); Interval: between initial irradiation and diagnosis RAOC
*Data not stated; †Extradural mass, thoracal spine.

cases and radiologically in 2 cases (range: 2–12 cm, median: 5.5 cm.).

6 patients were smokers, 8 were non-smokers; smoking habits were unknown in 2 patients. Alcohol ingestion was a known factor in 13 cases; only 2 patients consumed one or more units on a daily basis. In addition, 1 of them had a family history of oesophageal carcinoma: two first-line relatives having died from this disease.

In none of our patients were there other possible aetiological factors, such as Plummer–Vinson syndrome, achalasia, tylosis or lye ingestion involved.

Surgery results

Only 2 of 16 patients were eligible for surgery with curative intent. Both were in adequate physical condition and had small (2–3 cm), well or moderately differentiated squamous cell carcinomas of the proximal oesophagus; no signs of local invasion and/or metastases were found, either pre- or intra-operatively.

Oesophagectomy was followed by radiotherapy in 1 case when the pathology report revealed tumour cells up to 1 mm of the resectional margins (case 1, Table 2). As this patient had a history of mediastinal irradiation, she received a lower total dose than usually applied in these cases: 41 Gy was administered in fractions of 1.5–1.75 Gy, twice daily, over a period of 19 days. Survival in this particular case exceeded 5 years.

Oesophageal resection in the second patient (case 2, Table 2) was complicated by anastomic leakage. Treatment was conservative (nill by mouth, nasogastric suction, antibiotics). Eventually, a severe stricture developed at this level associated with a fistula to the neck. The latter closed spontaneously in due time; repeated dilatations, initially with an interval of 10 days, were required to maintain food passage through the fibrotic cervical anastomosis. This situation improved gradually: 2 years after resection a 2-month interval was sufficient. Now, over 38 months following surgery, this patient is alive and well without signs of recurrence; oesophageal dilatation is performed every 6–8 months.

Oesophageal resection was not an option in 14 patients for the following reasons: local invasion: 5 patients; lymph node metastases in neck/abdomen: 2 patients; age, poor physical

Table 2. Characteristics and treatment in 16 patients with radiation-associated oesophageal cancer

Patient	Age	Sex	Initial lesion†	Initial radiation dose (Gy)	Interval (years)	Localisation‡	Length oesca. (cm)	Additional treatment§	Survival (months)
Surgery									
1	34	f	HD	40	11	Prox	3	Radioth. 41 Gy	> 60
2	45	f	Breast carcinoma	35	2	Prox	2	Dilatation	> 38
Full dose radiotherapy								Endoprosthesis	
3	58	f	Breast carcinoma	*	5	Mid	6	Gastrostomy	12
4	49	f	Larynx carcinoma	47	17	Prox	5	—	2
5	36	f	Goiter	*	40	Prox	*	—	11
6	54	m	Thyreotoxicosis	*	36	Prox	6	Gastrostomy, VCR +	4
7	70	m	Tuberculosis	*	63	Prox	*	BLEO + MTX + FA(4×)	13
Limited radiotherapy‖									
8	73¶	f	Breast carcinoma	50	6	Prox	5	—	3
9	72¶	m	HD	*	44	Dist	7	Endoprosthesis	13
10	46**	f	Layrnx carcinoma	40	9	Prox	5	MMC + VDS(1×)	3
Dilatation and stenting									
11	83	f	NHL	40	4	Dist	12	—	4
12	63	m	Larynx carcinoma	*	36	Prox	7	—	10
13	76	m	Lung carcinoma	53	8	Prox	6	—	6
14	34	m	Lung carcinoma	*	9	Mid	8	CDDP + VDS(3×)	7
Chemotherapy									
15	32	m	HD	42	15	Prox	5	Dilatation, gastrostomy	27
16	58	f	NHL	40	6	Prox	3	—	2

*Data not stated. †HD = Hodgkin's disease; NHL = non-Hodgkin lymphoma; ‡prox, mid, dist = proximal, middle, distal section of the oesophagus respectively; §VCR = vincristine; BLEO = bleomycin; MTX = methotrexate; FA = leuvocorin; MMC = mitomycin-C; CDDP = cisplatinum; VDS = vindesine; indicated between (): number of cycles received; ‖intraluminal ¶ or low dose external beam**.

condition or tumour size: 6 patients. 1 patient (case 3, Table 2) initially refused to undergo any invasive measure, including surgery; whether oesophagectomy would have been at all possible in her case is doubtful, given the size of the tumour involved (length: 6 cm.). 3 patients required palliative surgery in the form of a gastrostomy; in 2, this was performed on admission, in a third after failure of other therapeutic measures (case 15, Table 2).

Radiotherapy results

Radiotherapy was considered in all 14 patients not eligible for surgery; 4 were rejected immediately in view of the total dose of irradition previously administered (cases 11–14, Table 2); 2 patients were excluded when involvement of the trachea was demonstrated, which made them high-risk cases for fistula formation (cases 15 and 16, Table 2).

In 5 cases, full external beam radiotherapy courses were planned (60 Gy in 6 weeks). This group included 3 patients, initially treated for benign lesions, hence it was assumed that the dose administered then had been relatively low (cases 5–7, Table 2); patients 3 and 4, however, received curative dosages for malignancy in the past; additional full dose radiotherapy was unavoidable in patient 3—as mentioned earlier, she rejected all invasive measures which left only one course of action open to us. Patient 4 (Table 2) required a gastrostomy on short notice as the oesophagus was found to be completely blocked by tumour; in view of the severity of her situation, intensive treatment seemed justified; irradiation resulted in relief from dysphagia for 2 months, but had to be discontinued after 32 Gy due to rapid deterioration of her clinical condition. The duration of responses in other patients treated with external beam radiotherapy was somewhat longer: up to 10 months after initiation of treatment.

Radiotherapy was a limited option in 3 patients: 2 were eligible for intraluminal irradiation (high or medium dose rate technique, cases 8 and 9, respectively) (Table 2). Only the patient treated with medium dose rate intraluminal irradiation experienced some relief from dysphagia for a period of 2 months; a poor physical condition prevented a second attempt. In a third case (case 10, Table 2), low dose external beam irradiation (2 × 10 Gy) was applied as a final palliative measure after failure of chemotherapy, but proved to be unsuccessful.

Serious complications did not occur in any of the 8 patients treated with radiotherapy.

Results of oesophageal stenting and/or dilatations

Oesophageal stenting and/or dilatation, either as a primary or secondary palliative measure, was applied in 7 patients, resulting in adequate palliation for up to 10 months. Insertion of an endoprosthesis, under normal circumstances one of the mainstays of palliative treatment in oesophageal carcinoma, was often prevented by proximal localisation of the tumour: stenting at this level frequently causes an irritating globus sensation, or, occasionally, tracheal compression and dyspnoea.

Chemotherapy results

As a last resort, 5 patients were treated with chemotherapy. The basis regimen was a combination of cisplatinum, vindesin, bleomycin or mitomycin C; however, due to impaired renal or pulmonary function, either cisplatinum or bleomycin had to be omitted in most cases.

Chemotherapy was the initial treatment of choice in two patients (case 15: three cycles of cisplatinum + vindesin; case 16: 1 cycle of cisplatinum + vindesin + bleomycin); patients 7,

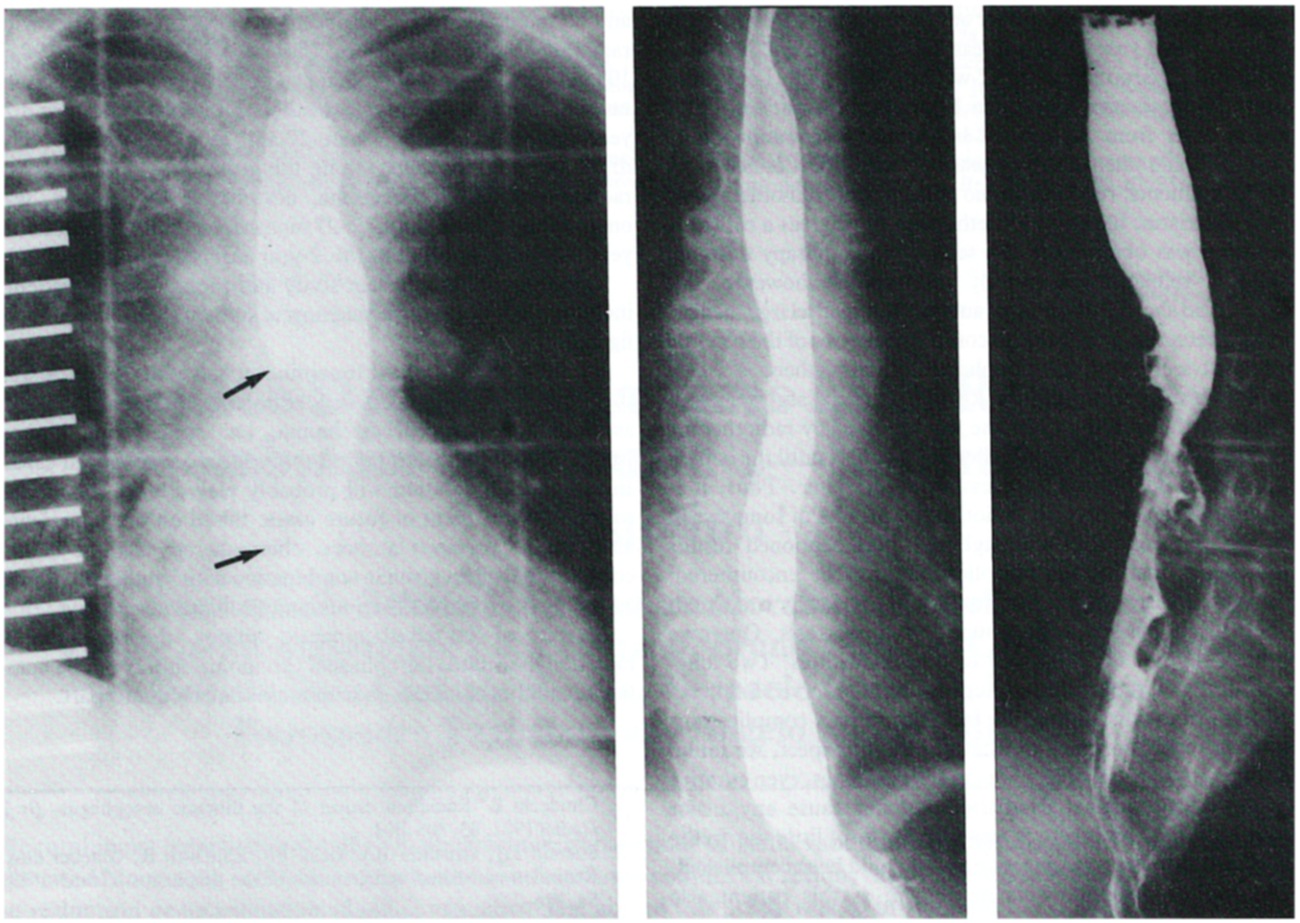

Fig. 1. Radiation-associated squamous cell carcinoma of the oesophagus in a 58-year-old woman (case 3). Left: barium-swallow at presentation with superimposed field for external beam radiotherapy. Middle: complete disappearance of tumour 3 months later. Right: 10 months after presentation: stenosis, deep ulceration and necrosis, either due to radio-necrosis or recurrent disease.

10 and 14 received combination chemotherapy after failure of other palliative procedures (for details see Table 2).

A response was observed in only 1 case (number 7, Table 2), although it was only short-lasting (2 months) and subjective in nature; endoscopical assessment after four cycles of vincristin, bleomycin, methotrexate and leucovorin revealed only a no change status; in addition, a tracheo-oesophageal fistula developed.

The clinical course of patient number 15, Table 2, was particularly remarkable: he did not respond to chemotherapy and required a gastrostomy 17 months after diagnosis; nevertheless, he survived for another 10 months without any further therapy; thus, he is the longest survivor among the 14 patients not eligible for surgery. The overall median survival for this group was 6.5 months.

DISCUSSION

The clinical picture of radiation-associated oesophageal carcinoma as observed in our patients was largely similar to that reported by previous authors.

In most cases, a long latent interval elapsed between initial irradiation and diagnosis of (predominantly squamous cell) carcinoma of the oesophagus [literature: 3–52 years, median 14 years (Table 1); our series: 2–63 years, median 8.5 years]. In comparison with the literature (median age: 66 years), our patients were relatively young (median age: 56 years). Both values are at the opposite ends of the 55–65 year spectrum, generally cited as the age that most non-radiation-associated (NRA) oesophageal malignancies are diagnosed in the western world [21].

There appear to be two more or less distinct patterns of presentation. The majority of the patients reported thus far was first seen with a 1–6 month history of dysphagia; radiological and endoscopic findings were usually consistent with malignancy, a diagnosis readily confirmed by biopsies; only two authors reported false negative initial biopsies, suggesting merely inflammatory changes [1, 4].

5 of the 16 patients presented with complaints of chronic intermittent dysphagia which had been present for a period of up to 3 years. 3 similar cases were described by previous authors; on one occasion, the onset of dysphagia could be traced back as far as 10 years [11, 13].

Such a clinical course suggests a gradual development of chronic, radiation induced inflammation into malignancy; in the earlier stages of transition, differentiation of these conditions appears to be difficult; in all cases with this type of presentation, repeated biopsies were required, even in the presence of a clinical picture highly suggestive for malignancy.

Although most of the publications presently available deal extensively with the clinical features of radiation-associated oesophageal carcinoma, reports of therapeutic efforts are rare. Some authors merely state that patients were referred for surgery, without indicating the eventual outcome of the procedure [4, 9, 11]. However, follow-up is given in 2 cases pub-

lished by Sherrill *et al.* [2]; after oesophagectomy, 1 patient was alive and well 1 year later, whereas the second patient died from anastomotic disruption within 2 weeks. Chudecki [1] described successful resectional surgery in 1 case, but the patient died 3 months later from myocardial infarction. A combination of irradiation and chemotherapy was applied by O'Connell *et al.* [13] in 2 patients, resulting in 'no change' in 1 (radiotherapy 25 Gy + vincristin, bleomycin, methotrexate) whereas a complete remission was observed in the second (radiotherapy dose not stated + velban, cisplatinum); unfortunately however, this patient died shortly afterwards; autopsy revealed a large mediastinal abscess, apparently due to complete necrosis of the recently irradiated section of the oesophagus. Finally, there is a case reported by Marchese *et al.* [17], where unsuccessful treatment with cisplatinum and vinblastine was followed by radiotherapy (24 Gy), resulting in (partial) relief of dysphagia until the patient was dead from tumour progression 1 year later. Thus, it is suggested that surgery and radiotherapy may be of some use in treating this condition, although the aforementioned results also suggest that serious complications may be encountered: anastomotic disruption due to surgery in previously irradiated, hence poorly vascularised, tissue, or radionecrosis. Our own findings support the feasibility of both modalities. Two long-term survivors, the first ever described, were observed following resection, notwithstanding the fact that serious complications arose in 1 case. Contrary to what one might expect, we found radiotherapy to be relatively safe; in selected cases, even curative dosages of mediastinal irradiation did not cause any major complication. Chemotherapy was found to be of little use; in the only case where some (subjective) relief could be accomplished, a tracheo-oesophageal fistula developed; as this patient also received high dose irradiation, it is conceivable that this complication occurred as a result of enhanced tissue damage due to combined radio- and chemotherapy. Oesophageal necrosis, observed by O'Connell and colleagues [13] in a patient similarly treated, may have been based on the same mechanism.

The disappointing results of intraluminal irradiation can to some extent be attributed to the fact that this modality was still in its developmental stage when we were conducting this study; experience recently gained in our institution with the (high dose rate) intraluminal technique in (NRA) oesophageal carcinoma (unpublished) is, however, encouraging. The major advantage of this approach is a high local tumour dose with rapidly falling irradiation levels beyond the oesophagus; a highly desirable feature, especially in previously irradiated patients. We expect to see better results from intraluminal radiotherapy in the future, due to both improved technical skills and the fact that more patients will be eligible for irradiation.

In comparison with results observed after treatment of (NRA) oesophageal malignancies, our patients did not fare badly in terms of survival. Calculated over the whole group of 16 cases, the 1- and 2-year survival proportions were 32 and 19%, respectively (Kaplan–Meier survival analysis). Based on a study of 83 783 previously published cases of (NRA) squamous cell carcinoma of the oesophagus, Earlam and Cunha-Melo [22] estimated that out of every 100 patients visiting a doctor with this type of malignancy, only 18% might be expected to survive 1 year, whereas the predicted 2-year survival proportion was merely 9%. A recent (unpublished) review of patients, treated in our institution for (NRA) oesophageal carcinoma revealed 108 cases presenting with malignancy of the squamous cell type between 1984 and 1989; 10 tumours were resected, resulting in survival ranging from 1 to 48 months (median: 13 months); 38 and 60 months survival, as observed in the present series with radiation-associated carcinoma, fits well within this range; 98 or 108 patients were not eligible for surgery. Survival in this group ranged from 1 to 49 months (median: 7 months); the 1- and 2-year survival proportions were 27 and 15%, respectively. The difference with findings among the group of 14 patients with radiation-associated carcinoma, not eligible for surgery, was only slight (survival range: 2–27 months, median 6.5 months; 1-year survival proportion: 21%, 2-year survival proportion: 7%).

The design of the present study and the number of patients included does not allow a meaningful statistical analysis of these figures.

For the present, we have to confine ourselves to the conclusion that they seem to support our treatment policy for radiation-associated oesophageal carcinoma, i.e. surgery for limited tumours, external beam radiotherapy for more advanced cases. Intraluminal irradiation will probably play a more substantial role in the treatment of future cases. Based on our experience and that of previous authors, chemotherapy cannot be recommended; when given in combination with irradiation, it may even enhance the risk of serious complications developing.

In spite of limited therapeutic options, the prognosis of radiation-associated oesophageal carcinoma appears to be comparable to that of its non-radiation-associated counterpart.

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Low-dose Dopamine Induces Early Recovery of Recombinant Interleukin-2—Impaired Renal Function

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Recombinant interleukin-2 (rIL-2) can produce impairment of renal function with hypotension, fluid retention, elevated blood urea nitrogen, oliguria and low fractional sodium excretion; these side-effects are a common cause of reduction or interruption of rIL-2 infusion. The aim of this study was to investigate the control and treatment of renal toxicity induced by rIL-2 therapy. Here we show that dopamine, at a low dose of 2 μg/kg/min, completely prevented renal toxicity induced by rIL-2. While continuing rIL-2 therapy, 24-h continuous infusion of low-dose dopamine produced a rapid normalisation of urine output and a significant decrease in serum creatinine levels and body weight ($P < 0.01$), with an early and complete recovery of the rIL-2—impaired renal function: mean recovery time of renal function in patients treated with dopamine was significantly lower ($P < 0.05$) than in non-treated patients (4.8 days vs. 10 days, respectively).
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INTRODUCTION

IMMUNOTHERAPY WITH recombinant interleukin-2 (rIL-2) has shown antitumour effects in patients with metastatic renal cell carcinoma or melanoma. The best results (35% overall response rate) have been achieved with high dosage of rIL-2 (100 000 Cetus units/kg every 8 h for 5 days, followed by 7–10 days of rest, and a further 5 days of therapy) and reinfusion of *in vitro* activated LAK (lymphokine-activated killer) cells [1, 2]. Results achieved with high-dose rIL-2 alone, without reinfusion of LAK cells, seem comparable, although fewer complete responses have been observed. A 19–20% response rate has also been achieved with rIL-2 alone at a lower dose (3 million Cetus units/m^2/day for 5 days, followed by a 6-day break and a further 4.5 days of therapy), in intravenous continuous infusion [3, 4, 5].

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It must be considered, however, that important side-effects often determine reduction or discontinuation of rIL-2 administration. A major side-effect of rIL-2 therapy is the vascular leak syndrome (VLS), which is due to an increase of vascular permeability and is characterised by hypovolaemia, hypotension, oedema, increase of body weight and acute renal failure [6]. These side-effects are dose-dependent, disappear when rIL-2 treatment is discontinued and can sometimes be extremely severe and life-threatening; continuous patient monitoring or admission to intensive care units is often required.

This report describes a new approach for the achievement of complete control of renal toxicity through the use of low doses of dopamine (2 μg/kg/min).

Dopamine effects are mediated by at least three types of vascular receptors, including adrenergic and dopaminergic receptors, through various dose-related mechanisms [7]. At the dose employed, dopamine does not alter blood pressure, but acts as a renal vasodilator and increases renal blood flow [8, 9], which is often reduced during rIL-2 treatment [10, 11]. Early recovery of renal function can, therefore, be achieved, and dose-reduction of rIL-2 is avoided.