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Original Paper

Concurrent Radiotherapy and Continuous Ambulatory Infusion 5-Fluorouracil in Advanced Head and Neck Cancer

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Patients with locally advanced stage 3 or 4 recurrent squamous cell carcinoma of the head and neck received 5-fluorouracil (5-FU) 200 or 300 mg/m^2/day by prolonged ambulatory infusion concomitantly with radiotherapy (60–66 Gy) to the primary site and neck nodes in 30–33 fractions at five fractions per week, boosting to smaller volumes after 60 Gy. Of 39 patients, the complete response rate was 82% (95% CI: 67–93%). The estimated percentage without failure at 2 years was 59% (S.E. 8%) and at 4 years was 50% (S.E. 8%). Estimated head and neck cancer specific survival was 64% (S.E. 8%) at 2 years and 52% (S.E. 8%) at 4 years. Acute toxicities included moist desquamation in 49% and dry desquamation in 28%, confluent mucositis in 56% and patchy mucositis in 44%. Late effects, more than 6 months after completing treatment, assessed in 35 patients, included severe salivary dysfunction in 3 patients and moderate in 21, severe osteonecrosis in 4 patients and moderate toxicity in subcutaneous tissues in 13, skin in 3 and mucosa in 2 patients. It is feasible to give continuous 5-FU concurrently with radiotherapy in locally advanced or recurrent head and neck cancer, albeit with increased toxicity. The response rate and survival obtained in this trial justify further investigation of the combined treatment in a randomised trial.

Key words: 5-fluorouracil (5-FU), radiotherapy, continuous infusion, head and neck cancer
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INTRODUCTION

PATIENTS WITH advanced inoperable head and neck cancer have a limited response to radiation therapy. Based on 1516 patients from the Radiation Therapy Oncology Group Cancer Registry and the control arm of randomised studies 79–13 and 79–15, a complete response occurs in 97% of patients with T_1N_0 disease but only 33% of those with T_4N_3 tumours [1].

Strategies for improving this result include changing the fractionation schedule or combining chemotherapy with radiation therapy. In combined modality treatment, the use of sequential chemotherapy and radiotherapy as part of the treatment regimen has shown varying results but, in general, is not superior to radiation without chemotherapy, in phase III studies [2–4].

Clinical trials testing concomitant chemo/radiotherapy in head and neck cancer have been more promising. Lo and colleagues [5] reported that both local control and survival were improved in a randomised trial, adding bolus 5-fluorouracil (5-FU) to radiation therapy in advanced squamous cell carcinoma of the oral cavity and oropharynx. The difference was only statistically significant in patients with oral cavity tumours. Improvements in local control have been reported when single agent bleomycin, cisplatin and mitomycin C are given concomitantly with radiation [6–8]. Drug combinations, such as the commonly used cisplatin and 5-FU regimen, have been given concomitantly with radiation, and in a randomised study in head and neck cancer, concomitant delivery of this regimen was superior to sequential chemotherapy and radiation [9, 10]. Giving chemotherapy concomitantly with radiation increases the toxicity of the treatment and can compromise the delivery of the radiation.

Byfield and colleagues examined the pharmacological requirements for obtaining sensitisation of cells to combined 5-FU and X-rays [11]. They concluded that 5-FU radiosensitisation was a postradiation phenomenon, with enhanced cytotoxicity dependent on both 5-FU concentration and duration of exposure, suggesting that infusion was superior to bolus and that beneficial effects would be maximal in tumours at least partially sensitive to 5-FU. They designed a study in

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advanced head and neck cancer where 5 day infusions were given with 4 daily fractions of radiation repeated 5 times with intervals of at least 9 days to allow toxicity to resolve. There was a 75% response rate for stage IV patients without significant enhancement of toxicity [12]. 5-Fluorouracil could be given with each fraction of conventionally fractionated radiotherapy if 5-FU was delivered by prolonged infusion. Furthermore, there were already examples of prolonged infusions of 5-FU showing advantages over bolus schedules [13]. A pilot study of prolonged infusion 5-FU 200–300 mg/m^2/day delivered by portable infusion pumps demonstrated the feasibility of combining this with a course of conventional radiotherapy of up to 65 Gy delivered at 1.8–2.0 Gy/day for a range of malignancies [14].

This study further investigates the feasibility of combining prolonged ambulatory infusions of 5-FU with conventionally fractionated radiotherapy of 60–66 Gy for patients with advanced head and neck cancer.

PATIENTS AND METHODS

Study design

The study was designed to assess the efficacy of the combined treatment by determining the response rate, remission duration and survival, and to assess the toxicity of concurrent combined therapy. A maximum of 40 patients presenting at the Peter MacCallum Cancer Institute (PMCI) were to be entered on the trial. They were required to have measurable or evaluable locally advanced squamous cell carcinoma of the oral cavity, pharynx or larynx, no prior chemotherapy or radiotherapy, no distant metastases, ECOG performance status 0–2, adequate bone marrow function with pretreatment haemoglobin of $\geq$ 100 g/l, leucocyte count $\geq 3 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, serum creatinine < 0.15 mmol/l and adequate liver function with serum aspartate aminotransferase (AST) less than twice the upper limit of the normal range. No other serious concomitant medical or psychiatric illness or prior or concomitant malignancy was allowed. The Ethics Committee of the PMCI approved the study and each patient gave voluntary written informed consent before entering the study.

Patient population

Of the 44 patients registered in the trial, 5 were excluded from analysis because of other prior or concomitant malignancy (3), adenocarcinoma not squamous cell (1), or low platelet count (1). The remaining 39 patients are considered in this paper.

Of the patients, 35 had no prior surgery and 4 had recurrences in the oral cavity following surgery (Table 1). Of the 35 newly diagnosed patients, 6 had cancers of the oral cavity, 8 of the nasopharynx, 16 of the oropharynx, 2 of the hypopharynx and 3 of the larynx. Of the 35, 8 presented with stage 3 disease and the remainder with stage 4. All patients had ECOG performance status of 0–1.

Treatment plan

The 5-FU was initially planned to be administered at a dose of 200 mg/m^2/day, but was increased to 300 mg/m^2/day after the first 2 patients. Subsequently, 2 further patients were prescribed 5-FU at 200 mg/m^2/day in error. It was given as a continuous infusion through a Hickman's catheter using an ambulatory infusion pump. The chemotherapy infusion was commenced immediately following the first radiation dose and continued throughout the radiotherapy until 24 h after the final radiation fraction. It was planned to discontinue both the infusion and radiation if grade 4 toxicity occurred.

Table 1. Patient characteristics

	New cases (35)	Recurrent (4)
Sex		
Males	30	3
Females	5	1
Age		
Median	55	51.5
Range	21–74	40–71
Performance status		
ECOG 0	24	1
1	11	3
Differentiation		
Well	1	2
Moderate	13	1
Poor	10	1
Undifferentiated	5	0
Unknown	6	0
Site		
Oral cavity	Stage 3 1 T_3N_1	4
	Stage 4 1 T_2N_2	
	1 T_4N_0	
	2 T_4N_2	
	1 T_4N_1	
Nasopharynx	Stage 3 1 T_3N_0	0
	Stage 4 2 T_2N_2	
	3 T_3N_2	
	2 T_4N_0	
Oropharynx	Stage 3 3 T_3N_0	0
	3 T_3N_1	
	Stage 4 2 T_2N_2	
	1 T_2N_3	
	3 T_4N_0	
	3 T_4N_1	
	1 T_4N_2	
Hypopharynx	Stage 4 1 T_2N_2	
	1 T_4N_2	
Larynx	Stage 4 1 T_1N_2	
	2 T_2N_2	

Radiotherapy treatment technique involved the construction of an immobilisation cast of Cobex. Sterile stainless steel "seeds" were inserted submucosally at the perimeter of the accessible tumours to assist tumour localisation simulation. Radiation therapy was delivered by 6 MV linear accelerator to a prescribed mean tumour dose of 60–66 Gy in 30–33 fractions treating 5 fractions per week. Wedges and/or tissue compensators were used to minimise dosage variation throughout the irradiated volume. Cord dose was limited to 45 Gy, although small volumes were treated to a maximum dose of 50 Gy. Patients undergoing elective irradiation of the lower neck received 50 Gy in 25 fractions. All patients undergoing irradiation of the oral cavity and/or at risk of significant xerostomia underwent dental assessment prior to therapy.

In patients who relapsed above the clavicles after a complete response, the radiotherapy technique used was re-evaluated to

determine the relationship of the recurrent disease to the radically treated volume, i.e. whether it lay within or marginal to it.

Assessment

Complete response (CR) was defined as the disappearance of all clinical evidence of tumour for at least four weeks. All patients were reviewed weekly during the therapy. Acute radiation reactions in skin and mucosa and symptoms related to them were scored on separate scales. Following completion of treatment, patients were assessed monthly for the first year, every two months for the second year, every three months for the third year, then every four to six months thereafter.

At each visit, the patient was examined for the extent of tumour and intensity of acute reactions until they had resolved. In the majority of patients, clinical examination was sufficient to determine the presence or absence of disease, but CT scanning was used where this approach was inadequate, particularly for nasopharyngeal tumours. Assessment of late radiation effects commenced 6 months after the completion of radiotherapy. A simple scoring system was devised (0 = no detectable change to 3 = severe late radiation effect) to record changes in skin, subcutaneous tissue, mucosa, bone/cartilage and salivary function.

Statistical methods

All patients were followed up to 10 August 1993 (close-out date). Survival was measured from the date of commencement of chemo/radiotherapy. Survival curves were estimated using the Kaplan–Meier product-limit method with censoring of the survival of living patients at the close-out date [15]. For overall survival curves, all deaths were counted. For head and neck cancer specific survival curves, patients who died of other causes with no evidence of head and neck cancer were censored at their dates of death. For time to failure curves (disease-free survival), persistent disease, local or distant relapse following CR, or death due to treatment were counted as failures; time to failure was taken as zero for patients with persistent disease. Patients who died of other causes or who were still alive without relapse were censored at their dates of death and the close-out date, respectively.

The cumulative incidences of local failure (including persistent disease, local relapse following CR and treatment-related death) and distant metastases were estimated using the method of Kalbfleisch and Prentice [16]. The sum of the two cumulative incidences at each time point is equal to 100% minus the estimated percentage failure free at the same time point.

The Kaplan–Meier product-limit method was also used to estimate the duration of moderate or severe acute skin or mucosal toxic effects. Moderate or severe skin toxicity was defined as dry or moist desquamation, respectively, and moderate or severe mucosal toxicity was defined as patchy or confluent mucositis, respectively. Duration of toxicity was measured from the date it was first recorded as moderate or severe until the date when it was finally recorded as only mild (erythema) or resolved. Patients who died early or whose assessments for toxicity became irregular were censored at the date of their last toxicity assessment at which moderate or severe toxicity was still present. The Brookmeyer–Crowley method was used to estimate 95% confidence intervals for median durations [15].

RESULTS

Dose delivery

Of the patients, 34 (87%) received the radiotherapy as planned. There were 5 new patients who received less than 60 Gy to the primary site, 4 stopping at 36 Gy, 40 Gy, 56 Gy or 58 Gy because of toxicity, and one stopping at 54 Gy to avoid exceeding cord tolerance. Of the patients, 72% were given radiotherapy to the neck in a separate field with all but 2 patients receiving at least 50 Gy. Radiotherapy was given over a period of 23–54 days, median duration 44 days.

Of the patients, 7 received less than 90% of the planned 5-FU dose, including 2 who received only 36 Gy or 40 Gy of radiotherapy. Six stopped early because of toxicity: 3 with the hand/foot syndrome, 1 with a painful rash and 2 with local skin and mucosal effects of the combined treatment, 1 patient withdrew from the trial early for reasons unrelated to toxicity.

Acute toxicity

The major acute toxicity in the irradiated area was mucositis, with 22 patients (56%) with confluent mucositis or severe oedema (Table 2) and the remaining 17 patients (44%) with patchy mucositis. Most of the former required nasogastric tubes for feeding. Similarly, 19 patients (49%) had moist desquamation of the skin and 11 (28%) dry desquamation. The estimated median duration of patchy or confluent mucositis was 2.1 months (95% C.I. 1.6–2.5 months), with a maximum of 6.3 months. The estimated median duration of dry or moist desquamation of the skin was 1.1 months (95% C.I. 0.9–1.8 months), maximum 3.2 months with the exception of 1 patient whose toxicity was still present after 12.9 months.

The major systemic toxicities of 5-FU were hand/foot syndrome, which occurred in 8 patients but was only severe in 1, and an erythematous rash on the torso or legs which was observed in 4 patients but again only severe in 1. Gastrointestinal toxicity included 7 cases graded as having severe vomiting and 1 with severe diarrhoea. Constipation was only mild (8 patients) or moderate (11 patients). No severe myelosuppression was recorded.

Late effects

Of the 39 patients, 4 died of head and neck cancer within 6 months of radiotherapy and had no opportunity to develop late effects (Table 3). Although dry mouth was the most common late effect, it was only severe in 3 patients and moderate in 21. Severe osteoradionecrosis was recorded in 4 patients while the worst mucosal or cutaneous toxicities were graded as moderate. All patients resumed oral nutrition.

Response and survival

The complete response rate was 82% (95% C.I. 67–93%) and was achieved in 30 of the 35 new cases and 2 of the 4 patients with recurrent disease. All the patients with nasopharyngeal cancer had a complete response. The median follow-up, by the close-out date, for patients still alive was 55 months (range 48–72 months).

Of the 32 complete responders, 11 relapsed. The site of first recurrence was in the site of the primary in 2, the neck in 4 and distant metastases in 5. 8 patients eventually developed distant metastases, 1 in bone, 3 in lung, 1 in subcutaneous nodules, 1 in nodes and liver, 1 in bone and neck and neck nodule and 1 whose sites of relapse were unknown. Only 1 patient was given salvage treatment which was chemotherapy for metastases.

Table 2. Acute toxicities of treatment

Local toxicities		Number of cases (total 39)
Skin		
None		0
Erythema		9
Dry desquamation		11
Moist desquamation		19
Mucosa		
None		0
Erythema		0
Patchy mucositis/mild oedema		17
Confluent mucositis/severe oedema		22
Symptoms of mucositis*		
None		0
Mild		6
Moderate		16
Severe		17
Systemic toxicities		
Hand/foot syndrome		
None		31
Mild		2
Moderate		5
Severe		1
Rash (torso, legs)		
None		35
Mild		1
Moderate		2
Severe		1
Nausea and vomiting		
None		17
Mild	Nausea only (WHO grade 1)	6
Moderate	Transient vomiting (WHO grade 2)	9
Severe	Vomiting requiring therapy (WHO grade 3)	7
Diarrhoea		
None		31
Mild	Transient < 2 days (WHO grade 1)	4
Moderate	Tolerable but > 2 days (WHO grade 2)	3
Severe	Intolerable needs therapy (WHO grade 3)	1
Constipation		
None		20
Mild	(WHO grade 1)	8
Moderate	(WHO grade 2)	11

*Symptoms of mucositis: mild symptoms, normal or soft diet, intake maintained; moderate symptoms, soft or liquid diet, required medication to maintain intake; severe symptoms, unable to maintain oral intake, required admission ± nasogastric tube ± treatment break.

Table 3. Late effects of treatment

Late effect	Number of cases (total 35*)
Skin	
None	15
Mild	15
Moderate	3
Unknown†	2
Subcutaneous	
None	5
Mild	14
Moderate	13
Unknown	3
Mucosa	
None	19
Mild	12
Moderate	2
Unknown	2
Salivary function	
None	3
Mild	6
Moderate	21
Severe	3
Unknown	2
Bone	
None	28
Severe	4
Unknown	3

* 4 cases who died within 6 months of completing radiotherapy.
† All late effects for 2 patients were unknown.

26 patients (67%) have died and the remaining 13 patients (33%) were alive without disease at the close-out date. 7 patients died from other causes with no evidence of head and neck cancer (3 primary lung cancer, 1 cirrhosis of liver, 1 acute myocardial infarction, 1 coronary occlusion and 1 unknown cause with no evidence of head and neck cancer 6 days before death). The two cardiac related deaths occurred 17.5 months and 43.9 months after commencing treatment. One other patient died as a result of a haemorrhage from a radionecrotic area in the mouth, 28 months after commencing chemo/radiotherapy. He had no evidence of head and neck cancer at the time of his death. For all patients, the estimated 2 year overall survival was 59% (S.E. 8%) and 4 year survival was 41% (S.E. 8%). Estimated head and neck cancer specific survival was 64% (S.E. 8%) at 2 years and 52% (S.E. 8%) at 4 years. For previously untreated cases, estimated head and neck cancer specific survival was 68% (S.E. 8%) at 2 years and 55% (S.E. 9%) at 4 years. Among the new cases, the estimated 4 year survival in stage 3 patients was 70% (S.E. 18%) and in stage 4 patients 51% (S.E. 10%; Figure 1).

The estimated percentage of patients who were failure free at 2 years was 59% (S.E. 8%) and at 4 years 50% (S.E. 8%) (Figure 2). The cumulative incidence of local failure as the first failure was estimated to be 31% (S.E. 7%) at 2 years and 37% (S.E. 8%) at 4 years. The cumulative incidence of distant metastases as the first failure was estimated to be 10% (S.E. 5%) at 2 years and 14% (S.E. 6%) at 4 years.

Of the 7 patients who received less than 90% of the prescribed radiotherapy or chemotherapy, 1 suffered early death from head and neck cancer and 4 failed locally. The remaining 2 had lasting responses, but 1 died of another cause.

3 of the 4 patients who were prescribed 5-FU at 200 mg/m^2/day had complete responses, but 1 subsequently relapsed in the nodes marginal to the radiotherapy field.

DISCUSSION

This study demonstrates that 5-FU can be delivered continuously throughout a course of radiotherapy fractionated once daily for head and neck cancer. Although the local acute

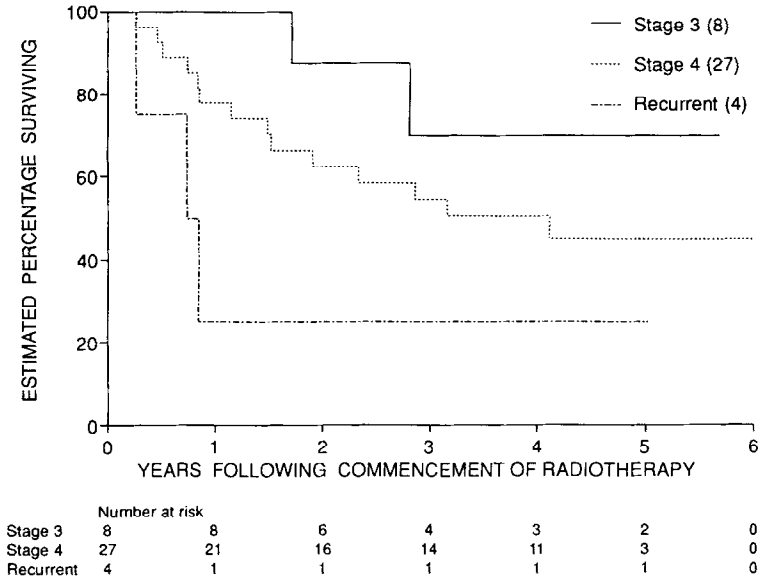

Figure 1. Head and neck cancer specific survival.

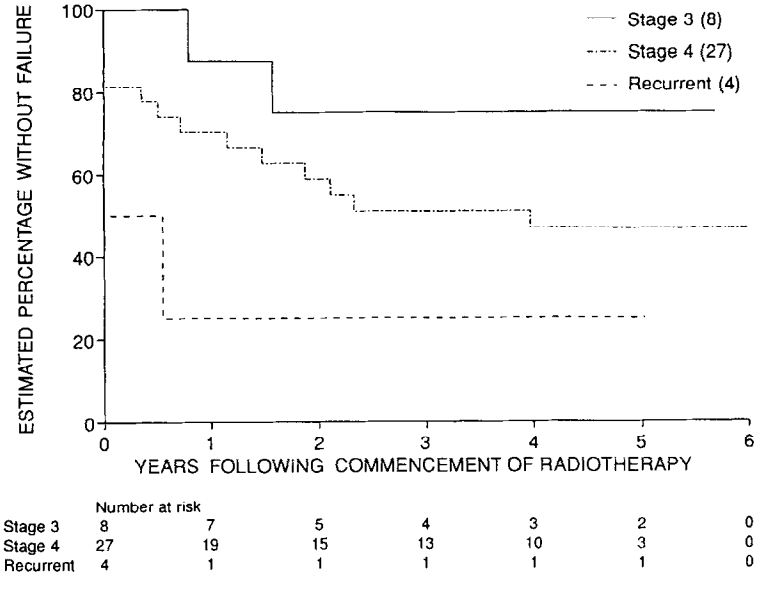

Figure 2. Time to failure.

toxicities were more severe and more prolonged than we expected from our experience with radiation alone, the tissues recovered well with few severe late effects in skin and mucosa. Despite dental intervention, osteonecrosis is a risk of radiation alone in patients with head and neck cancer who often have long-standing poor oral hygiene and dentition.

The use of indwelling venous access devices in this patient population could be problematic. The commonest complications expected are catheter related infetions or thromboses. We attribute the lack of serious problems with the catheters in this trial to the close supervision of the patients as they presented for 5 days of each week for radiotherapy and the relatively short time during which the catheters were required, since they were removed as soon as practicable following the completion of therapy.

The 4 year head and neck cancer specific survival of 51% for stage 4 patients (44% overall survival) and the observation that most of the deaths occurred in the first 2 years is encouraging, as it has previously been reported that no more than 1–2% long-term survivors are seen in this group [17]. Historical data from PMCI, using the same radiation schedule without chemotherapy, show a 4 year head and neck cancer specific survival of 20% for 19 stage 4 patients compared with 51% in this study.

Eligible patients were entered as they presented. There were only 3 patients treated with laryngeal cancer, yet 8 patients with nasopharyngeal cancer formed a good prognostic group as evidenced by all having complete responses to therapy. Nonetheless, the excellent survival achieved across the whole group of patients encourages us to suggest that a randomised

study of continuous infusion 5-FU and radiation compared with radiation alone would be warranted in advanced head and neck cancer.

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