Fast neutron treatment for squamous cell carcinoma of the head and neck: final report of Edinburgh randomised trial

R Hugh MacDougall, J Archibald Orr, Gillian R Kerr, William Duncan

Abstract

Objective—To compare neutron treatment and megavoltage (photon) radiotherapy in locally advanced squamous cell carcinoma of the head and neck.

Design—Randomised trial of patients stratified by site of primary tumour and presence or absence of lymph node metastases. Follow up of patients after treatment.

Setting—Department of clinical oncology, Western General Hospital, Edinburgh.

Patients—165 Patients with untreated, histologically proved squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx. All patients completed treatment, and no patient was lost to follow up.

Intervention—Treatment with either neutrons or photons.

Main outcome measures—Disease state and morbidity (scored with the system of the European Organisation for Research on Treatment of Cancer) at each visit during follow up.

Results—Of the 165 patients, 85 were randomised to receive neutron treatment and 80 to receive photon treatment. Minimum follow up was five years. Local control of cancer remained similar in the two groups, being achieved in 37 (44%) patients after neutron treatment and 36 (45%) after photon treatment. Five year and actuarial 10 year survival rates were 24% (20/85) and 14% respectively in the group treated with neutrons and 34% (27/80) and 30% respectively in the group treated with photons. Five year survival rates without local disease were 19% (16/85) and 30% (24/80) respectively. Necrosis was more common after neutron treatment than after photon treatment. Seven patients in the neutron group who developed necrosis died whereas no deaths were associated with photon treatment.

Conclusion—Rates of long term local control were similar in the two groups. Necrosis related to radiation was more common in patients treated with neutrons, and the mortality related to treatment was significantly higher in these patients.

Department of Clinical Oncology, Western General Hospital, Edinburgh EH4 2XU
R Hugh MacDougall, FRCR, *consultant radiation oncologist*
J Archibald Orr, FRCR, *consultant radiation oncologist*
Gillian R Kerr, MSC, *lecturer in medical statistics*
William Duncan, FRCR, *professor of radiation oncology*

Correspondence to:
Dr MacDougall.

Br Med J 1990;301:1241-2

Introduction

This paper reports the results of a long term follow up of patients admitted to a randomised trial at the Medical Research Council's cyclotron unit in Edinburgh from 1977 to 1984. In 1987 we reported details of the selection and characteristics of patients, randomisation, treatment techniques, doses, and fractionation schedules.[1] The trial was undertaken after a report of improved control of advanced head and neck cancer after neutron treatment at the Medical Research Council's cyclotron unit at Hammersmith Hospital, London.[2] It was designed to include some patients with less advanced disease than that of patients recruited to the London trial so that long term local control of cancer and morbidity could be more accurately assessed. The fractionation schedule was identical for both groups. It was decided that the neutron doses used in Edinburgh should be, on average, 5% lower than those used at Hammersmith Hospital because of the high morbidity recorded there.[3]

The estimation of the size of the trial was based on a predicted enhancement of local control of cancer from 40% (found with photon treatment in Edinburgh) to 70% (found with neutron treatment at Hammersmith Hospital). It was calculated that 164 patients were required if this difference was to be significant ($\alpha=0{\cdot}02$, power 90%) in a two tailed test of significance.

Patients and methods

Patients who had untreated, histologically proved squamous carcinoma in the oral cavity, oropharynx, larynx, or hypopharynx were eligible. They had to be under 80 years old and judged fit for a radical course of radiotherapy. All patients were assessed initially by a referring otolaryngologist or oral surgeon and then by at least two of the radiation oncologists responsible for this study before they were judged suitable for inclusion in the trial. Written informed consent was obtained from all patients. Overall, 165 eligible patients were analysed; 85 were treated with neutrons and 80 with photons. The distribution of patients by age, site, and T and N classification of tumours and nodes was similar in the two groups.[1]

All treatments were given in 20 daily fractions over four weeks. The total absorbed dose ($n+\gamma$) of neutrons ranged from 15·6 Gy to 16·7 Gy and that of photons from 54 Gy to 56 Gy, depending on the site and the size of the field. All patients completed treatment as planned.

Follow up assessment was carried out at intervals defined by the protocol by the same team of radiation oncologists. Disease state and morbidity (scored with the system of the European Organisation for Research on Treatment of Cancer[4]) were assessed at each visit. The minimum follow up was five years and the maximum 11 years. No patient was lost to follow up.

Results

Long term rates of local control were similar in the two groups (table I). Overall, 37 of the 85 patients (44%) treated with neutrons and 36 of the 80 patients treated with photons had sustained local control. The 95% confidence interval for the difference of 1% in favour for photon treatment was large (−14% to 17%). There was no significant difference in control rates by site.

Two apparent late recurrences of tumours within the

TABLE I—*Rates of local control and occurrence of necrosis by site of tumour in patients treated with neutrons or photons (percentages of patients in parentheses)*

Site	Neutron treatment			Photon treatment		
	No of patients	Local control	Necrosis	No of patients	Local control	Necrosis
Oral cavity	32	12 (38)	8 (25)	34	15 (44)	3 (9)
Oropharynx	21	9 (43)	4 (19)	14	6 (43)	2 (14)
Larynx	21	11 (52)	4 (19)	22	12 (55)	3 (14)
Hypopharynx	11	5 (45)	2 (18)	10	3 (30)	1 (10)
Total	85	37 (44)	18 (21)	80	36 (45)	9 (11)

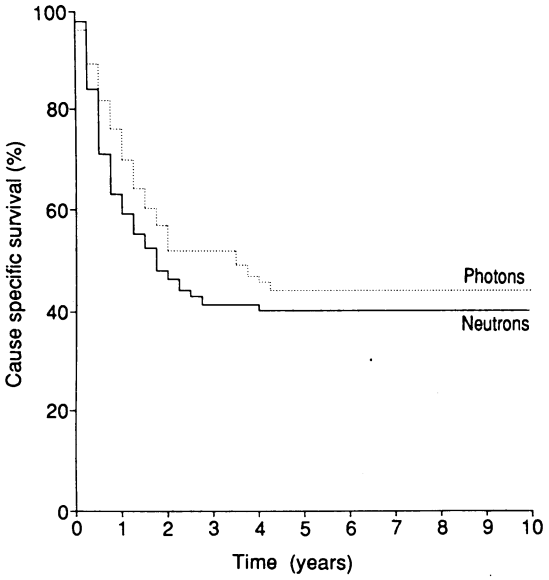

FIG 1—*Actuarial cause specific survival rates in patients treated with photons or neutrons*

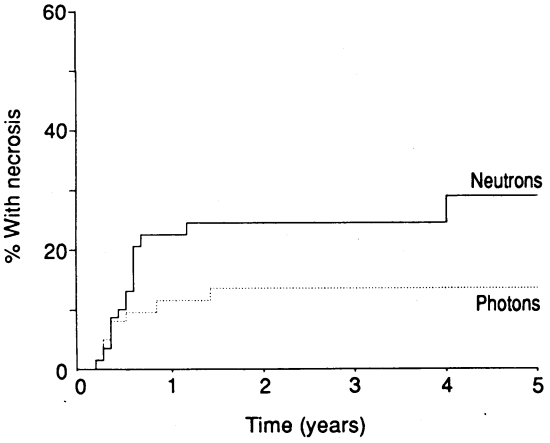

FIG 2—*Cumulating incidence of necrosis in mucosa or laryngeal cartilage in patients treated with photons or neutrons*

treated area were seen in the group treated with neutrons, one seven years and one nine years after treatment. The histological features of one of these tumours was completely different from those of the original tumour. Immunohistochemical studies suggested a mesenchymal origin, and a presumptive diagnosis of soft tissue sarcoma was made. No late recurrences were seen in the patients treated with photons.

The five year survival rate was 24% after treatment with neutrons (20/85) and 34% after treatment with photons (27/80). The actuarial 10 year survival rates were 14% and 30% respectively (p=0·07, log rank test). The survival rate without local disease at five years was 19% (16/85) (95% confidence interval 11% to 27%) for patients treated with neutrons and 30% (24/80) (20% to 40%) for those treated with photons. Figure 1 shows the actuarial cause specific survival rates up to 10 years (p=0·35, log rank test).

In the group treated with neutrons 18 patients developed late radiation necrosis (grade 4, European Organisation for Research on Treatment of Cancer system) in the mucosa or laryngeal cartilage compared with nine patients in the group treated with photons (table I). Figure 2 shows the cumulative incidence of necrosis, calculated by the inverted life table method. At two years the incidence was 25% in the group treated with neutrons and 13% in the group treated with photons, and at five years the figures were 29% and 13% respectively (p=0·07, log rank test). Although the rate of necrosis in the two groups was not significantly different, the subsequent mortality was significantly higher in the patients treated with neutrons. Seven patients treated with neutrons who developed late radiation necrosis were judged to have died as a direct consequence. One of these had necrosis of the mandible. None of the patients treated with photons died as a result of late radiation necrosis. Table II shows the outcome in patients who developed necrosis by treatment.

TABLE II—*Outcome in patients who developed necrosis by treatment*

Outcome	Neutron treatment	Photon treatment	Total
Alive:			
Healed or conservative treatment	3	2	5
After surgery	2	2	4
Dead:			
Intercurrent disease	2	2	4
Recurrent cancer	4	3	7
Radiation necrosis	7		7
Total	18	9	27

Discussion

There is no evidence in this study of a therapeutic advantage for treatment with neutrons. Tumour control rates and cause specific survival rates were similar in the two groups. Control of tumours after photon treatment (45%) agreed with the expected results used in the design of the trial (40%), but control after neutron treatment (44%) did not reach that predicted by the study at Hammersmith Hospital. The late recurrence of a tumour in one patient and apparent sarcoma in another in the irradiated area in the group treated with neutrons are unusual. The diagnosis of soft tissue sarcoma is a cause for concern as it may be related to the treatment using high linear energy transfer neutrons.

Although the overall rate of necrosis was not significantly worse in the patients treated with neutrons, a significant difference in mortality related to treatment was seen. Despite giving a lower dose of neutrons than that at Hammersmith Hospital we also found a high mortality related to treatment, although it was less than that reported by the Medical Research Council's working group in its assessment of the Hammersmith Hospital study.[4]

The original study was supported by the Medical Research Council, Cancer Research Campaign, Scottish Home and Health Department, and Lothian Health Board. Follow up was supported by the Medical Research Council.

1 Duncan W, Orr JA, Arnott SJ, Jack WJL, Kerr GR, Williams JR. Fast neutron therapy for squamous cell carcinoma in the head and neck region: results of a randomised trial. *Int J Radiat Oncol Biol Phys* 1987;13:171-8.
2 Catterall M, Sutherland I, Bewley DK. First results of a randomised clinical trial of fast neutrons compared with x or gamma rays in treatment of advanced tumours of the head and neck. *BMJ* 1975;i:653-6.
3 Catterall M, Bewley DK, Sutherland I. Second report on results of a randomised clinical trial of fast neutrons compared with x or gamma rays in treatment of advanced tumours of head and neck. *BMJ* 1977;i:1642.
4 Medical Research Council Neutron Therapy Working Group. A comparative review of the Hammersmith (1971-1975) and Edinburgh (1977-1982) neutron therapy trials of certain cancers of the oral cavity, oropharynx, larynx and hypopharynx. *Br J Radiol* 1986;59:429-40.

(Accepted 14 September 1990)