PAPERS AND ORIGINALS

First Results of a Randomized Clinical Trial of Fast Neutrons Compared with X or Gamma Rays in Treatment of Advanced Tumours of the Head and Neck

Report to the Medical Research Council

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Summary

Results of the first randomized clinical trial to compare the effects of fast neutrons and those of x or gamma rays (photons) in treating patients with advanced tumours of the head and neck are reported. In 37 out of 52 patients treated with neutrons and 16 out of 50 treated with photons the local tumour completely regressed; the tumour later recurred in nine of the 16 photon patients but in none of the 37 neutron patients. The advantages to the neutron-treated patients were statistically highly significant and were seen in tumours of well and poorly differentiated histology and in each site. Complications after treatment did not differ significantly between the groups. Despite these substantial differences in local control of the tumour there were no significant differences in mortality between the series.

A detailed study of the effective doses and the response of tumours and normal tissue in each series indicated that the improved results from neutron therapy were due to differences in the biological quality of the beam and not to the rather higher average effective dose in the neutron series. To assess the long-term effects of neutron treatment patients in earlier stages of disease and with smaller tumours should be included in the next phase of the trial.

Introduction

Many primary tumours are still incurable by radiotherapy despite many improvements in technique. Further refinements in treatment planning or to the machines delivering x and gamma rays are unlikely to have a significant effect on this problem. Fast neutrons involve different biological responses¹ and their use is an attempt to improve the effect on the tumour relative to the surrounding normal tissues.

Fast neutrons from the M.R.C. cyclotron have been used for treating various advanced tumours in 350 patients with encouraging results.²⁻⁴ A randomized clinical trial has been set up to compare fast neutrons with photons (gamma rays from cobalt-60 or megavoltage x rays). This trial is being made in patients with advanced tumours of the head and neck because most of these tumours can be seen and palpated, and recurrences are quickly apparent. The response of the normal tissues to the two types of radiation can also be observed and compared. The aim of the trial is to compare the effects of initial treatment with a radical dose of neutrons with those of a radical dose of photons. Any supplementary treatment may be given later, as needed by the patient. We present here an interim report.

Patients and Methods

ELIGIBILITY FOR THE TRIAL*

To enter the trial a patient had to have an advanced tumour in the head or neck (excluding the brain), histologically confirmed and with no known distant metastases and no previous radiotherapy in the site of the malignancy. Tumours were staged according to the TNM classification by U.I.C.C.⁵; patients with tumours in stage T₃ or T₄ with or without nodes or T₁ or T₂ with nodes were eligible. Most of the patients submitted to the trial had such extensive tumours that six sites were used for analysis: buccal cavity, oropharynx, hypopharynx (including cervical oesophagus, larynx and pyriform sinus), antrum and nasopharynx, salivary glands, and cervical nodes where the

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*Full details of the protocol are available on request.

primary tumour had apparently been cured. Patients with reticuloses or lymphoepithelioma were not eligible and there have so far been no cases of sarcoma.

PATIENTS

Patients were submitted from London, Birmingham, and south-east England. They were randomized in such a way that both treatment groups were similar in site, stage, histology, previous surgery, or chemotherapy (see table I).† All patients allocated to neutron therapy were treated at Hammersmith Hospital and were then referred back to their original hospital for follow-up. Patients allocated to treatment with photons were usually treated at their own hospital and were followed up there. Through this collaborative scheme useful numbers of patients were included in a reasonable time.

Between July 1971 and May 1974 107 patients were admitted to the trial, 55 being allocated to the neutron and 52 to the photon series. Five were excluded from analysis; four (two on neutrons, two on photons) because they died during treatment and one because the tumour was found to be secondary to a primary elsewhere. The progress of these 102 patients was assessed up to June 1974. The numbers followed for different periods in each series are given in fig. 1.

TREATMENT

Fast Neutrons.—Patients were treated three times weekly for four weeks and the total tumour dose was 1440 rads. This total dose was adjusted by a modified Ellis formula⁶ for a few patients for whom the overall time of 26 days had to be prolonged. The neutrons have a mean energy of 7.5 MeV and the beam is fixed and horizontal. It is therefore technically inferior to the photon beam from cobalt-60 or megavoltage machines, which can rotate around the patient. Furthermore, the penetration of the neutron beam compares badly with that of the cobalt or 6-MeV linear accelerator beam; at 8 cm in tissue the dose is reduced to 55% of the maximum compared with 75% from a 6-MeV linear accelerator.

Photons.—Patients were treated with Cobalt-60 gamma rays or x rays from a linear accelerator. The regimens of treatment varied according to local policy at different centres. Tumour doses ranged from 4540 rads in 12 fractions over 28 days to 6840 rads in 30 fractions over 43 days.

Management.—Radiotherapy was usually completed in four to six weeks after randomization, and no chemotherapy or surgical treatment was given for a further six weeks. Thereafter any further treatment for recurrent or metastatic tumours was given according to patients' needs.

Response to Treatment.—We considered that a tumour had regressed completely only if there was no sign of tumour by palpation, radiological examination, or inspection by more than one clinician. When induration was present this was termed incomplete regression or residual tumour. Recurrence was diagnosed if the tumour reappeared or if a residual tumour showed signs of extension.

†Details of the method of randomization are obtainable on request.

FIG. 1—Percentages of patients with persistent complete regression of tumours, regression followed by recurrence, incomplete regression, or death according to interval since the start of treatment (actuarial estimates).

Results

The local tumour regressed completely after treatment in 37 of the 52 patients treated with neutrons and there were no recurrences. Of the 50 photon patients 16 showed complete regression, but in nine the tumour recurred. The advantage to the neutron series applied to each site and for both well and poorly differentiated tumours (table I).

The cumulative percentages of patients who had shown complete regression, month by month from the start of treatment, were estimated by actuarial methods which took account of the different lengths of follow-up of each patient and used all the information available by the end of June 1974. The differences in the cumulative percentage curves for complete regression and in those for recurrence between the two series were each significant at the 0.1% level, using the logrank test.⁷ Fig. 1 shows the mortality in the two series and the local tumour response of the survivors and shows clearly the difference in local tumour response in the two series.

Pain was relieved in 37 out of 41 patients in the neutron series and 18 out of 33 in the photon series. It recurred in two of the 37 neutron patients and 10 of the 18 photon patients.

Patients Treated at Hammersmith.—Thirty-four patients (16 on neutrons, 18 on photons) were submitted for treatment at Hammersmith Hospital whether neutron or photon therapy was allocated. Before the end of June 1974 local tumours regressed completely in 14 patients on neutron therapy and six on photon therapy. The difference between the cumulative percentage curves was significant at the 1% level. The tumours recurred in three of the six photon-treated patients but in none of the 14 neutron-treated patients; this difference was significant at the 2% level.

Complications after treatment were noted in 22 neutron-treated patients and 21 photon-treated patients (table II). Most complications

TABLE I—Local Tumour Response to Neutron and Photon Treatments according to Site and Histological Classification of Tumour

		No. of Patients	Incomplete or No Regression	Complete Regression	
				No.	No. with Recurrence
Site of Tumour					
Buccal cavity	Neutron	15	3	12	0
	Photon	16	12	4	3
Oropharynx	Neutron	11	4	7	0
	Photon	11	6	5	1
Hypopharynx (including larynx)	Neutron	8	2	6	0
	Photon	11	7	4	2
Antrum and naso-pharynx	Neutron	7	2	5	0
	Photon	5	3	2	2
Cervical lymph nodes	Neutron	9	4	5	0
	Photon	5	4	1	1
Salivary glands	Neutron	2	0	2	0
	Photon	2	2	0	—
Histological Classification of Tumour					
Well differentiated	Neutron	34	11	23	0
	Photon	31	20	11	6
Poorly differentiated	Neutron	16	4	12	0
	Photon	17	13	4	2
Melanoma	Neutron	2	0	2	0
	Photon	2	1	1	1
All patients	Neutron	52	15	37	0
	Photon	50	34	16	9

TABLE II—Complications after Treatment

Complication	No. of Complications	
	Neutron Series	Photon Series
Aspiration	6	5
Laryngeal oedema	4	3
Fixed cords	2	1
Neurological complications	3	1
Haemorrhage	0	1
Necrotic ulcer	3	0
Dysphagia, stricture of oesophagus	1	2
Fibrosed salivary ducts	1	1
Dry mouth interfering with diet	2	3
Trismus	0	2
Major ophthalmic complication	1	1
Minor ophthalmic complication	1	3
Marked but symptomless subcutaneous fibrosis	1	1
Total	25	24
No. (%) of patients with complications	22 (42)	21 (42)

were in the larynx and pharynx, but many patients had had these symptoms before treatment and in some the tumours had already permanently distorted structures such as the constrictor muscles, posterior part of the tongue, and the epiglottis. In these cases the dysfunction remained even when there was no sign of tumour. Taking aspiration, laryngeal oedema, dysphagia, fibrosed vocal cords, and oesophageal stricture together, nine out of 19 neutron-treated and seven out of 22 photon-treated patients had such symptoms. Residual tumour was present, however, in only two of the nine neutron-treated patients but in five of the seven photon-treated patients. Of three necrotic ulcers (all in neutron-treated patients) two were small and healed with medical care.

Further Treatment to Primary Site.—Further treatment for control of the local tumour was given to 16 patients (two on neutrons, 14 on photons). The better local response in the neutron-treated series could not therefore be attributed to more treatment to the primary site in these patients. Four patients, all of whom had received photon treatment which had not controlled the tumour, were further irradiated. Six other patients in the photon series received chemotherapy for residual or recurrent tumours. Surgical excisions were required for residual or recurrent growths in six patients (two on neutrons, four on photons).

Deaths.—By the end of June 1974 25 of the 52 neutron-treated patients had died compared with 30 of the 50 photon-treated patients (see fig. 1). Most of the deaths were due to metastatic spread. This difference was not statistically significant (logrank test applied to the cumulative survival percentages).

Discussion

The patients in this trial had such advanced tumours that distant metastases usually became manifest within one year and were the commonest cause of death in both groups. Survival was therefore a less sensitive measure of effect than were the responses of the locally irradiated tissues.

The effective delivery of a uniform dose to the tumour, with the minimum radiation to adjacent normal structures, is the aim in radiotherapy and the neutrons from the Hammersmith cyclotron had three important disadvantages compared with x or gamma rays from modern machines. Firstly, the neutron beam was less penetrating and it was therefore necessary to use more fields with the neutron beam, which resulted in higher doses to the adjacent normal tissues. Secondly, the skin reactions produced by the neutrons added to the disadvantage of the large irradiated area. Thirdly, the fixed horizontal neutron beam meant that most of the patients had to be treated in the sitting position; this was difficult for several patients who were frail and had very large tumours. It is remarkable that in spite of these disadvantages neutrons were more successful than photons in all sites in causing regression of tumours, relief of pain, and an absence of recurrences.

These improved results could be due to a quantitative difference, in terms of a higher effective dose being given to the neutron-treated patients, rather than to a qualitative biological difference between the two radiations. Nevertheless, when the doses given were reduced to a common basis by calculating the time-dose

factor (T.D.F.)⁸ only a slight correlation was found between tumour regression and dose in each series. Fig. 2 shows the effective dose of radiation given to each patient in terms of the T.D.F. The patients in the photon series received a lower average dose and a wider range of doses than those in the neutron series, the difference between the mean T.D.F. values being about 20%. But where the T.D.F. values for neutrons and photons overlapped—roughly 100-120—there was still a much greater degree of local control of the tumour in the neutron-treated series. Comprehensive statistical analysis has confirmed that the larger average dose received by the neutron series made only a small contribution to the improved results in that series. Furthermore, more radiation would have inflicted greater damage on the adjacent normal structures, but morbidity was not very different in the two series. Hence, the improved results in the neutron-treated series seemed to be due to the biological properties of fast neutrons rather than merely to the delivery of a greater effective dose to the tumour.

FIG. 2—Response to treatment according to dose given. Shaded areas represent number of patients with recurrence in the treated area or failure to regress completely, and show that there was no significant correlation between dose received and failure to cause complete regression.

It might be argued that the comparison would have been more precise if the photon and neutron doses in the two series had been given in the same number of treatments and over the same period of time. But as there is no consensus among radiotherapists as to the optimum treatment regimen with photons it was an advantage to compare the standard dose of neutrons with a range of photon doses considered to be the most suitable for their patients by several experienced radiotherapists. Among the 34 patients submitted for treatment at Hammersmith, where the regimens were similar in the two series, the substantial advantage to the neutron series still attained statistical significance.

The statistically significant improvement in the immediate response of the local tumour after treatment with neutrons raises two questions: firstly, what will be the late effects of fast neutrons on the normal structures, and, secondly, will the tumours recur?

The results indicate that patients with longer prognoses may be entered into the trial, which would enable these questions to be answered. Though such patients are eligible only one patient in stage T₁ or T₂ with nodes has so far been submitted. Such patients are treated in many centres by a modified course of photon radiotherapy followed by surgical excision or by surgery alone. It is therefore proposed to widen the scope of the trial so that radical treatment with neutrons can be compared with treatment with a combination of photons and surgery or with surgery alone, according to the choice of the individual co-operating centre.

With several cyclotrons being built or already operating in Europe, America, and Japan fast neutrons are no longer an experimental possibility but a future clinical reality. Their place in cancer therapy should be established as soon as possible.

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Brucellosis and Veterinary Surgeons

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Summary

Forty-six veterinary surgeons were given a full clinical examination, serological examination with estimates of immunoglobulins, and supplementary haematological and radiological investigations. Thirty-five complained of one or more symptoms, and eight had abnormal physical signs which might have been caused by infection with *Brucella abortus*, but neither serological test results nor immunoglobulin estimates bore any special relation to the clinical features. The soundest way of assessing ill health which had possibly been caused by brucellosis seemed to be thorough clinical examination and disregard of serological findings. Interpreting results by the usual serological tests in the absence of a clinical examination is probably of doubtful value and may even be misleading.

Introduction

Veterinary surgeons are at risk of infection with *Brucella abortus* because of repeated contact with brucella-infected cattle, and many investigations have been carried out to assess the extent of this infection and its effects on health. No investigation of any size, however, has been based on clinical examination; serological results have been related to information obtained from replies to a questionnaire or from visual appearances and answers to questions put when blood samples were taken. Some recent investigations^{1 2} have related the results of clinical examination to laboratory findings, but the numbers of subjects examined were too small for analysis. In an attempt, therefore, to study the effects of brucella infection more closely we decided to examine

as many as possible of the vets working within a 25-mile radius of Worcester and relate clinical findings to antibody levels as obtained by serological tests.

Methods

Of the 46 vets investigated 36 were engaged actively in cattle practice. Four (cases 12, 19, 31, and 36; table I) were officers in the veterinary service (Agricultural Development Advisory Service) of the Ministry of Agriculture, Fisheries, and Food and were at risk of infection because much of their time was spent investigating brucellosis in the field, which involved handling potentially infected material such as placenta or dead calves and the taking of blood samples. Three (cases 17, 27, and 28) worked in a veterinary investigation centre and were at risk of infection in the laboratory from handling samples and cultures, but since they also investigated brucellosis in the field they were exposed through handling infected animals or infected material. Three (cases 20, 24, and 38) had been engaged in small animal practice for at least two years before being examined but had worked with cattle before going over to small animals.

Almost all the vets in the area were asked to participate and of 49 asked 46 were able to take part in the survey, which was conducted from November 1971 to January 1974. Each vet was examined by a consultant physician who paid particular attention to present and past symptoms; details of veterinary training and practice; exposure to *B. abortus*; past proved or suspected acute brucellosis; occurrence of accidental inoculation with S.19 or 45/20 vaccine; occurrence of local allergy to brucellosis; and whether the vet believed he was suffering from some continuing illness caused by contact with *B. abortus*.

Radiological assessment consisted of straight x-ray examination of the chest, examination of the upper abdomen with the subject in a recumbent supine position to display spleen size, and further examination of bones and joints when there was clinical suspicion of disease. Erythrocyte sedimentation rate, Westergren (E.S.R.); haemoglobin concentration; and white cell count (W.B.C.) were measured. The serological tests used were the saline agglutination test (S.A.T.), the agglutination test with 0.05 M 2-mercaptoethanol in the tubes instead of normal saline (M.E.T.), the antihuman globulin test (A.H.G.),³ and the complement fixation test (C.F.T.).⁴ The sera were also examined for IgM, IgG, and IgA content by immunofluorescence.⁵

Results

Forty-six veterinary surgeons, aged from 23 to 58 years, were examined, and all but one (case 38) were men (table I).

Symptoms.—No form of check list or direct inquiry of particular symptoms was used. Eleven vets felt entirely well with no symptoms.

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