

## Complications following fast neutron therapy for head and neck cancer

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### Abstract

Serious complications resulting from the use of fast neutrons to treat head and neck malignancies are reported in 38 patients. The average interval between treatment and onset of complications was 5.5 years. Significant airways obstruction, requiring a tracheostomy, occurred in two patients, and a gastrostomy or pharyngostomy was performed for intractable dysphagia in six. Eight patients developed osteoradionecrosis; carotid artery rupture occurred in three patients following surgery for residual or recurrent disease.

Our experience suggests that complications following fast neutron therapy for head and neck tumours are more severe, more common and occur after a longer time interval than those seen following conventional radiotherapy. Subsequent surgery in the irradiated area is compromised by severely impaired wound healing. When radical surgery is necessary for residual or recurrent disease the entire volume of irradiated tissue must be removed if healing is to be achieved.

### Introduction

The neutron was discovered by Chadwick in 1932. It is an atomic particle present in all atomic nuclei except hydrogen, possesses no charge and has a mass slightly greater than that of the proton.

The first neutron treatments were given by Stone between 1938 and 1943, using the Berkeley cyclotron in California (Stone, 1948). His conclusions were generally unfavourable; the treatment resulted in such bad late sequelae relative to the few good therapeutic results obtained that the trial was discontinued. However, the trial was carried out before the radiobiology of neutrons had been properly investigated. It was not appreciated that normal tissues surrounding the tumour received an overdose of neutrons, nor was an allowance made for the exit dose, especially when parallel opposed fields had been used. Finally, it was not appreciated that there was a different effect of fractionation with neutrons relative to photons.

In 1955, the Medical Research Council built a cyclotron at the Hammersmith Hospital and this was extended in the early 1960's by the installation of a remote, fixed external target which allowed for the production of a fast neutron beam. The radiobiology of fast neutrons was studied on plant stock, HeLa cell lines and on pig skin and they have been used therapeutically at the Hammersmith Hospital since 1970. Altogether, over 1,500 patients, with tumours at various sites, have been treated at this centre.

In 1971, a clinical trial studying the efficacy of fast neutrons as the primary treatment of advanced (stage II, III and IV) tumours of the Head and Neck region was started at the Hammersmith Hospital. Seventy patients who

received this treatment in the initial randomized trial comparing fast neutron with photon irradiation were analyzed (Catterall *et al.*, 1977). This trial ran until 1976. Additional patients with head and neck malignancies were subsequently treated using fast neutrons between 1976 and 1984, when the cyclotron was shut down.

### Patients and complications

To date we have seen 38 patients who have developed significant complications resulting from fast neutron therapy used to treat their head and neck malignancies (Table I). All patients received their fast neutron radiotherapy at the Hammersmith Hospital between 1971 and 1984, and were referred directly to this department when their complications developed. Fourteen of them were among the 70 treated during the initial trial period, representing 20 per cent (14/70) of that group. The mean time delay before the manifestation of complications was 5.5 years (range 6 months—9.5 years). Subjectively, the complications were significantly more severe than those seen following conventional radiotherapy.

#### *1. Dysphagia and airways obstruction*

There were 23 patients in this group. Six of these patients required a gastrostomy or pharyngostomy for intractable aspiration or grossly impaired pharyngeal motility. A further 15 patients developed severe dysphagia. Videofluoroscopy, carried out in nine of them, demonstrated impaired bolus propulsion through the pharynx in every case (Alexander *et al.*, 1989). In eight patients there

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TABLE I  
COMPLICATIONS FOLLOWING FAST NEUTRON THERAPY

Dysphagia and airways obstruction	23 patients
No. requiring gastrostomy or pharyngostomy	6
No. requiring tracheostomy	2
Tissue necrosis	15 patients
Osteoradionecrosis	8
Cervical skin necrosis	3
Pharyngeal wall necrosis	2
Perichondritis of larynx	1
Radiation myelitis	1
Complications of surgical intervention	9 patients
Salivary fistula	7
(carotid artery rupture	3)
Cervical skin necrosis	2

Some patients had more than one complication.

was absent or delayed triggering of the swallow reflex and impaired protection of the larynx. Many more patients treated with fast neutrons for laryngeal or pharyngeal cancer developed significant chronic dysphagia which did not merit reporting here.

Tracheostomy was necessary in two patients because of *airways obstruction secondary to laryngeal fibrosis*.

### 2. Tissue necrosis

The onset of soft tissue necrosis was characteristically delayed by several years following the neutron therapy, and could be attributed to local trauma in only one case.

Osteoradionecrosis was seen in eight patients, each of whom developed a chronic intraoral or cutaneous sinus connecting with the dead bone. The mandible was involved in seven patients and the maxilla in one. Two patients with osteoradionecrosis of the mandible required surgical excision of the irradiated bone, and adjacent soft tissue, for the relief of severe pain. Both conservative sequestrectomy and hyperbaric oxygen proved disappointing in reversing the disease process and controlling local symptoms.

Cervical skin necrosis occurred in these patients, two of whom required surgical reconstruction of the defect using pedicled cutaneous or mycutaneous flaps. In one patient the skin defect failed to heal despite several attempts at surgical repair over a seven year period.

A salivary fistula occurred spontaneously in two patients who had not undergone prior surgery; one was pharyngocutaneous, the other orocutaneous (Fig. 1). Breakdown of the pharyngeal wall occurred without development of a fistula in a third patient. Surgical intervention was necessary in all three cases. A laryngectomy was required in another patient for severe perichondritis of the larynx.

Radiation myelitis and quadriplegia occurred in one patient after irradiation of a T<sub>3</sub>N<sub>0</sub> squamous carcinoma of the larynx.

### 3. Complications of salvage surgery for residual or recurrent malignant disease

Three patients developed oro-cutaneous and four pharyngocutaneous fistulae following surgery for residual or recurrent disease. Carotid artery rupture occurred as a direct result of the salivary fistula in three cases, and was a terminal event in each instance.

Severe neck skin necrosis was seen in two patients

whose cervical tissues never healed completely, in spite of several attempts to resurface the defect with pedicled tissue brought in from outside the irradiated field.

When resection of neutron irradiated tissue was necessary, the resection volume had to include the entire three dimensional field of irradiation. This was judged by photographs taken soon after the initial therapy which showed post irradiation skin changes. Healing did not occur if neutron treated tissue was sutured to itself or to a reconstructive flap brought in from outside the treatment area.

Histological study of neutron irradiated tissue provides objective evidence of tissue ischaemia. Gross fibrosis and disruption of elastic material in the soft tissues is associated with the appearance of abnormal fibroblasts, typical of those seen after conventional radiotherapy. However, the degree of vascular damage is more severe. Small arteries and arterioles consistently show endothelial proliferation, medial hyalinization and disruption of the internal elastic lamina. Stenosis and luminal occlusion are common, and may be followed by recanalization.

### Discussion

The place of fast neutron radiotherapy in the treatment of malignant disease in the Head and Neck region is, as yet, unproven. Although the Hammersmith experience was reported as being favourable another, multi-centre, trial failed to confirm any advantage to the use of neutron therapy in the treatment of advanced malignant disease in the Head and Neck (Duncan *et al.*, 1984). Experience both at the Hammersmith and at Edinburgh has shown that morbidity resulting from treatment with low energy neutrons is very significant (Medical Research Council Neutron Therapy Research Group, 1986). It is reasonable to ask therefore whether yet further evidence of damage is relevant to the current practice of treating patients with high energy neutrons.

Our data provide information about the severity of the complications but not about the overall incidence, although the 20 per cent complication rate in the original trial group of 70 patients gives an indication of this. It has been estimated that the incidence of serious late complications with high energy neutrons is about half that experienced with low energy neutrons (Griffin *et al.*, 1986). It is admittedly difficult to make comparisons but even if this were true it is doubtful whether such a reduction would result in complication rates that would be acceptable or

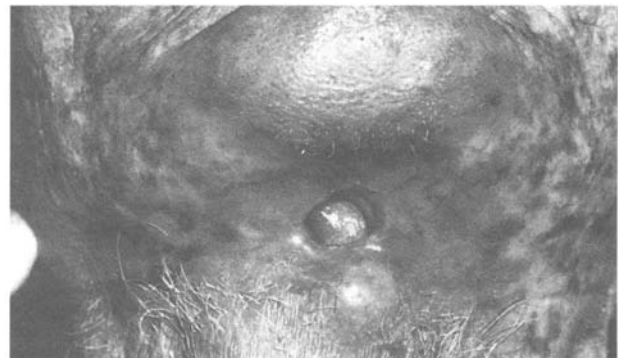


FIG. 1

Spontaneous orocutaneous fistula in an unoperated patient following fast neutron treatment.

indeed comparable to those encountered in conventional radiotherapy. One of the most worrying aspects of fast neutron treatment is that complications may continue to occur many years after treatment has been given. The long latent period is well illustrated in the group of patients referred to our unit where the mean interval was five and a half years. This particular feature applies to treatment with high energy as well as low energy neutrons (Cohen *et al.*, 1989), and it underlines the importance of an adequate period of follow-up before attempting to assess morbidity from this method of treatment.

There is now a substantial population of patients who have received fast neutron therapy for the treatment of head and neck tumours, and our experience has highlighted some of the problems these patients may present to the surgeon. This experience has led us to adopt guidelines for undertaking surgical treatment on patients who have been irradiated with fast neutrons:

- a. Conservative dental surgery should only be undertaken when absolutely necessary.
- b. Any surgical resection should include the entire volume of previously irradiated tissue.
- c. Wound healing takes 2 to 4 weeks.  
Surgery should be avoided whenever possible.

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