Fermi National Accelerator Laboratory

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# SECOND ANNUAL PROGRESS REPORT
# FERMILAB CANCER THERAPY FACILITY
# BATAVIA, ILLINOIS

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## INTRODUCTION

Following two years of preclinical studies (design, construction, and calibration and radiobiological studies invitro and in small animals), the physical and biological characterization of the beam was considered sufficiently advanced to commence treating patients in September, 1976. In the twenty-seven months of patient accrual since that date, a total of 424 patients were referred to the facility either for pilot studies or for critical evaluation in the cooperative clinical protocols (latest evaluation made in January 31, 1979). Of this total, 89 patients were unsuitable for evaluation (57 were not accepted for treatment because of medical or logistic considerations, 17 patients who were otherwise suitable elected not to participate, and 28 patients who commenced treatment were unable to complete the prescribed course). 285 evaluable patients were treated with neutrons and a further 43 are included in the study but were randomized for photon irradiation only. Currently, 22 additional patients (17 neutron and 5 controls) are on treatment (January 31, 1979). These figures provide a total of 350 evaluable cases of whom 225 were classified as pilot studies and 125 were entered into the national cooperative trials. The results of these trials are collated and evaluated by the Radiation Therapy Oncology Group located in Philadelphia, Pa.

The pilot studies include "protocol cases" who were not

eligible for statistical analysis because of experimental design exclusions (for example, not randomized, started before protocol activated, and noncompliance with prescribed eligibility requirement). The pilot studies provided information initially to confirm the efficacy and the safety of the beam in relatively advanced cases in whom the prospect of cure was considered remote, but also, more recently pilot studies for potentially curable radioresistent tumors. In the former instance information on normal tissue reactions was obtained and found to be essentially as expected on the basis of physical and radiobiological considerations. In the latter series the response of a variety of uncommon relatively radioresistent tumor types were studied.

The pilot studies could be crudely subdivided into the earlier palliative cases (phase I studies) and more recent radical treatments (phase II protocols). In each category there were patients treated with neutrons to full dosage, patients completing a preliminary course of photons referred for a neutron boost as a planned procedure, and patients previously treated with conventional photon irradiation who on subsequent recurrence were referred for a trial of neutrons.

The 97 protocol patients (phase III) studied during this period were predominately head and neck and intracranial tumors. The largest group comprised 44 nonresectable epidermoid carcinomas of the upper respiratory and alimentary tracts, and secondly, 31 patients with malignant gliomas (glioblastoma multiforme).

NEUTRON THERAPY TECHNIQUE

The facility was designed to provide the first isocentric

capability in the high LET field. Although we are constrained to a fixed horizontal beam, the intensity was high enough to allow placement of the patient at an adequate distance to permit the rotational and tranlational movements necessitated by isocentric set-up. At the present time, a source to isocenter distance of 153 cm is used. This distance will be increased to 190 cm in the near future to allow greater flexibility and dispense with the translation from x-ray to neutron isocenter. The isocenter is identified by four intersecting laser beams with which the patient is aligned. In general, the tumor is on the axis of rotation, and all of the movements, provided by conventional rotation isocentric therapy can be simulated with a vertical rather than a horizontal axis of rotation. Conventional fixation and immobilization procedures are used in this situation.

In general, radical neutron therapy was delivered over a nominal period of six weeks (treatment times range from 43 to 50 days). The number of fractions per week ranged from one to four as indicated either for convenience (in pilot studies) or as prescribed in the protocols (two to four fractions per week). The dosage and fractionation range considered to be biologically equivalent to 1900 ret (nominal standard dose) are shown in Table 2. It will be noted that the neutron dose changes relatively little with fractionation while the biologically equivalent photon exposure varies considerably in this regard. The RBE is considered to range between 2.5 for large, once weekly fractions to 3.0 for "daily"fractionation. Tumor doses, when neutrons were used alone, ranged between 2000 and

and 2400 neutron rads over the specified period of six weeks. In all other respects, the treatment plans were designed to match those which would be used in a conventional isocentric photon therapy set-up as closely as possible.

PLANNING, SIMULATION, AND SET-UP

The Fermilab neutron beam is fixed horizontally with a wide range of fixed size collimators made of polyethylene concrete. The colliators permit the use of wedges, shields, and bolus. The collimator angle can be adjusted by rotation coaxially with the central axis of the beam.

The patient sits in a chair or stands on a pedestal which can move in three dimensions and can rotate about a vertical axis through 360 degrees. The point of intersection of the vertical axis of rotation and the central axis of the beam provides a treatment isocenter analogous to that of a conventional rotation therapy machine. The treatment is usually carried out with the tumor at the axis of rotation of the chair. For larger field sizes or field sizes which do not match the collimators, the SAD may be varied or the treatment may be done at a corresponding source skin distance (SSD). The back and the headrest of the chair are made of aluminum and lucite. Various back and side supports are available to minimize the interactions of the beam with these fixtures. Lesions in the upper torso are treated with the patient sitting, those in the lower half are treated with the patient standing.

The patient planning, simulation, and set-up are done in the same treatment chair and room as patient therapy. The patient is immobilized using the conventional "Lightcast$^{R}$" method for head and neck irradiations and nylon straps for the

rest of the body. Laser beams and x-ray confirmation are used in treatment planning and set-up. The axis of rotation of the chair, the x-ray and the laser beams meet at the planning isocenter. The elevator is then lowered until the patient comes in front of the neutron beam. Laser beams at the treatment level meet at the isocenter and help in making any final adjustments. Neutrograms are used to confirm beam placement and direction in treatment position.

The treatment planning is done on a PDP-10 computer, programmed with capabilities to calculate and plot isodose distributions for fast neutrons and photon beams. The latter is especially important when patients are being treated with a mixed beam or neutron boost. Electron beam planning capability is still under development.

The photon radiation is delivered by the radiotherapist at the referring institution. There is excellent and close cooperation between the radiotherapists at the referring institution and those at the CTF. The success of the CTF is largely due to the active participation of various radiotherapists in this project. The patients are subsequently followed-up by all clinicians participating in the treatment.

## EVALUATION AND RESULTS

### Normal Tissue Tolerances

Acute reactions were recorded on all patients. Several interesting statements can be made at this stage. Firstly, no excessively severe acute reactions were observed in any patient. Skin and mucosal reactions were in general relatively mild and in only a few cases were significant painful or uncomfortable reactions produced. Secondly, the broad range of fractionation schemes described in Table 2 all lead to essentially similar acute reactions, confirming the expected weak dependence of radiosensitivity on fractionation per se with high LET particles. We are naturally aware of the possibility that late reactions may not correlate directly with acute reactions in this regard, and indeed, may be more severe with few fractions within the same overall treatment time. There has been insufficient follow-up to evaluate this effect at the present time, but the relatively small numbers of patients who have been followed for a year or more have so far not shown any ontoward late effects.

Late effects are being evaluated by observation at follow-up of a number of specific tissues traversed by the beam. These include:

1. Skin - Presumably because of the highly effective skin sparing effect of the high energy Fermilab neutron therapy beam, virtually no significant late effects in the skin, per se (as distinct from subcutaneous fascia) were observed. Late cutaneous telangiectasia, a common feature of low energy neutrons, was not observed in our series.

2. Subcutaneous Fascia - All patients surviving a year or more after radical dosage exposure show some degree of induration and fibrosis, which appears to be no more severe than that following a radical course of photon irradiation. Severe subcutaneous fibrosis, however, has been observed in those patients treated by full doses of neutrons for recurrence following full doses of photon irradiation.

3. Mucositis - Acute mucosal reactions were relatively mild. Acute confluent mucositis was observed uncommonly in some patients in whom it appeared not to be related to any differences in dosage, but could generally be attributed to heavy smoking during and after the course of treatment. It was noted that patients receiving the planned mixed beam procedure apparently had a more severe acute mucosal reaction than those getting pure neutron or pure photon treatment to equivalent doses. The magnitude and significance of this effect remains to be evaluated. All acute mucosal reactions have healed uneventfully and no late ulceration has been observed.

4. Xerostomia - Almost all patients irradiated in the head and neck region in whom the major salivary glands were included in the target volume experienced some degree of xerostomia and lost or altered taste. In some patients this response was severe and maintained. Many of these patients have not recovered completely during the observation period. Secondary nutritional disturbances following on the dry mouth and loss of taste have been encountered and alleviated to some

extent by careful dietary counseling.

5. Teeth and Mandible - All patients referred for irradiation of head and neck cancer had reasonably good dental hygiene by virtue of adequate preparation at the referring institution. No dental problems were encountered either during treatment or at follow-up in the patients treated to radical dosage more than six months ago. Particular attention was paid to possible late complications in the bone, but no patient in this group reported significant tenderness in the mandible or exhibited demonstrable x-ray changes even after high local dosage. It is concluded that the anticipated bone sparing effect of high energy neutron beams exists and in the absence of dental abnormalities, no problems in the mandible are likely to ensue.

6. Temporomandibular Joint - In many head and neck cases the beam traversed the ascending ramus of the mandible and the temporomandibular joint. Some degree of trismus is to be expected. Trismus to a minor degree has been observed in the majority of patients in whom both temporomandibular joints are within the target volume and in a few instances this has been severe. Trismus is considered a measurable evaluable endpoint and a careful dose effect study would seem to be in order in long term survivors in whom this tissue has been irradiated.

7. Spinal Cord - In the light of experience at other neutron therapy centers, the exceptional sensitivity

of the human spinal cord to neutron irradiation has been appreciated and steps taken to minimize or obviate this risk. Our convention is not to exceed 1250 neutron rads to the spine or if mixed beam therapy is used then the doses shall not exceed a total of $D_n + 0.25\ D_x \leq 1250$ rad (assuming a "worst case" RBE of 4). No case of spinal cord injury has been observed in this institution. Four patients in whom the spinal cord dose exceeded 1670 neutron rad have shown no evidence of cord damage up to two years after exposure. One patient had transient myelopathy (L'Hermitte's sign) for about one month after irradiation with 700 neutron rads following roughly 3000 photon rads (cobalt) to the cord.

8. Brain and Cranial Nerves - It is hardly possible to evaluate radiation damage to the central nervous system in the treatment of glioblastoma with the mixed beam protocol because of the difficulty in distinguishing effects attributable to the growth of the tumor, effects arising from the photon dosage delivered (5000 rads), and any effects which may be specific to the neutron beam. However, we have no clear evidence of neutron injury to the brain in any evaluable cases at the present time. In other head and neck protocols, cranial nerves are frequently irradiated to relatively high doses, and for this reason, patients are interrogated at follow-up in regard to paresthesia, anesthesia, and motor weakness. Positive replies to interrogation in this area have not been frequent. One case of facial nerve weakness and a

few paresthesias have been reported. Late effects are to be anticipated in this area and will be evaluated at follow-up.

9. Pharyngeal Musculature - Edema and fibrosis of the pharynx with consequent dysphagia is observed as a transient phenomenon in many patients irradiated for supraglottic tumors. One would anticipate that late effects in this region would lead to persistent dysphagia and other aberrations of deglutition. So far, dysphagia has been transient and no such long term effects have been observed although patients have been carefully interrogated in this regard.

10. Laryngeal Cartilage - Laryngeal cartilage necrosis has not been observed in our series.

11. Esophagus - Transient esophagitis has been observed in patients receiving radical irradiation of the chest (mainly for lung and esophageal cancer) but no follow-up information is available at the present time.

12. Lung Fibrosis - Relatively few patients have been treated for lung cancer and many of these too recently to evaluate pulmonary reactions. Of three patients treated one year ago as pilot studies on the protocol (currently active) one remains alive and symptom free without any evidence of pulmonary damage, one has died of disseminated metastases and at autopsy showed no evidence of primary lung cancer or of pulmonary radiation damage, and one died four months after treatment with a massive nonspecific pneumonia which could be attributed to an intercurrent viral infection,

radiation injury, or a combined effect of neutron irradiation and chemotherapy.

13. Intestine - Thirty-two (32) patients have been irradiated quite recently for intraabdominal lesions including the pancreas, rectum, bladder, and prostate. In all cases, the small bowel and sometimes the colon has necessarily been included in the target volume and has received the full prescribed tumor dose of 2000 to 2200 neutron rads in six weeks. Acute and late reactions may be anticipated in many cases from this regime. Surprisingly, acute reactions have not been observed. Apart from the relatively mild nausea in only a small proportion of treatment patients and moderate diarrhea in a few cases, no acute GI effects have appeared. Late effects have not been evaluable since relatively few long term survivors have accumulated in this series so far. It would not be surprising if some did occur. One patient provided information of considerable interest following irradiation with 2400 rads in six weeks for a massive recurrent carcinoma of the rectum. Eight months after irradiation this patient developed intestinal obstruction attributable to fibrosis of the ileum which progressed to the stage of necessitating surgical intervention. A segment of stenotic small intestine was resected, the anastomosis failed to heal, and the patient died of septic peritonitis. At autopsy the tumor was found to be completely ablated. This case should be classified as a lethal complication

of neutron irradiation of the small intestine. The incidence of this type of complication remains to be evaluated since the denominator in the equation will not be known until a considerable follow-up period has been obtained, but first impressions are that the rate will not be high.

TABLE I Evaluable Cases, Non-resectable Cancer of Head and Neck

ENT CASES

Neutrons only; doses over 2000n rads

| Stage* | Number of patients | Local control | NED | |
|---|---|---|---|---|
| III | 5 | 2 | 2 | |
| IV | 6 | 2 | 2 | |

Neutrons and photons, boost (5000p + 750n) and mixed (3/5p, 2/5n 6600 - 7400 rad eq.)

| | | | | |
|---|---|---|---|---|
| II | 4 | 3 | 4 | 1 local failure, retreated, now NED |
| III | 14 | 7 | 6 | 1 nodal failure |
| IV | 19 | 7 | 3 | 4 nodal failure |

Note: nodes not treated with neutrons in boost modality.

Retreated with neutrons after recurrence following photon irradiation

| | | | | |
|---|---|---|---|---|
| Late stages | 16 | 6 | 2 | 2 nodal failures, 2 distant metastasis with local control |

SALIVARY CASES

Neutrons only; doses over 2000n rads

| | | | |
|---|---|---|---|
| 6 | 3 | 3 | |

Photons and neutron boost

| | | | |
|---|---|---|---|
| 4 | 2 | 2 | |

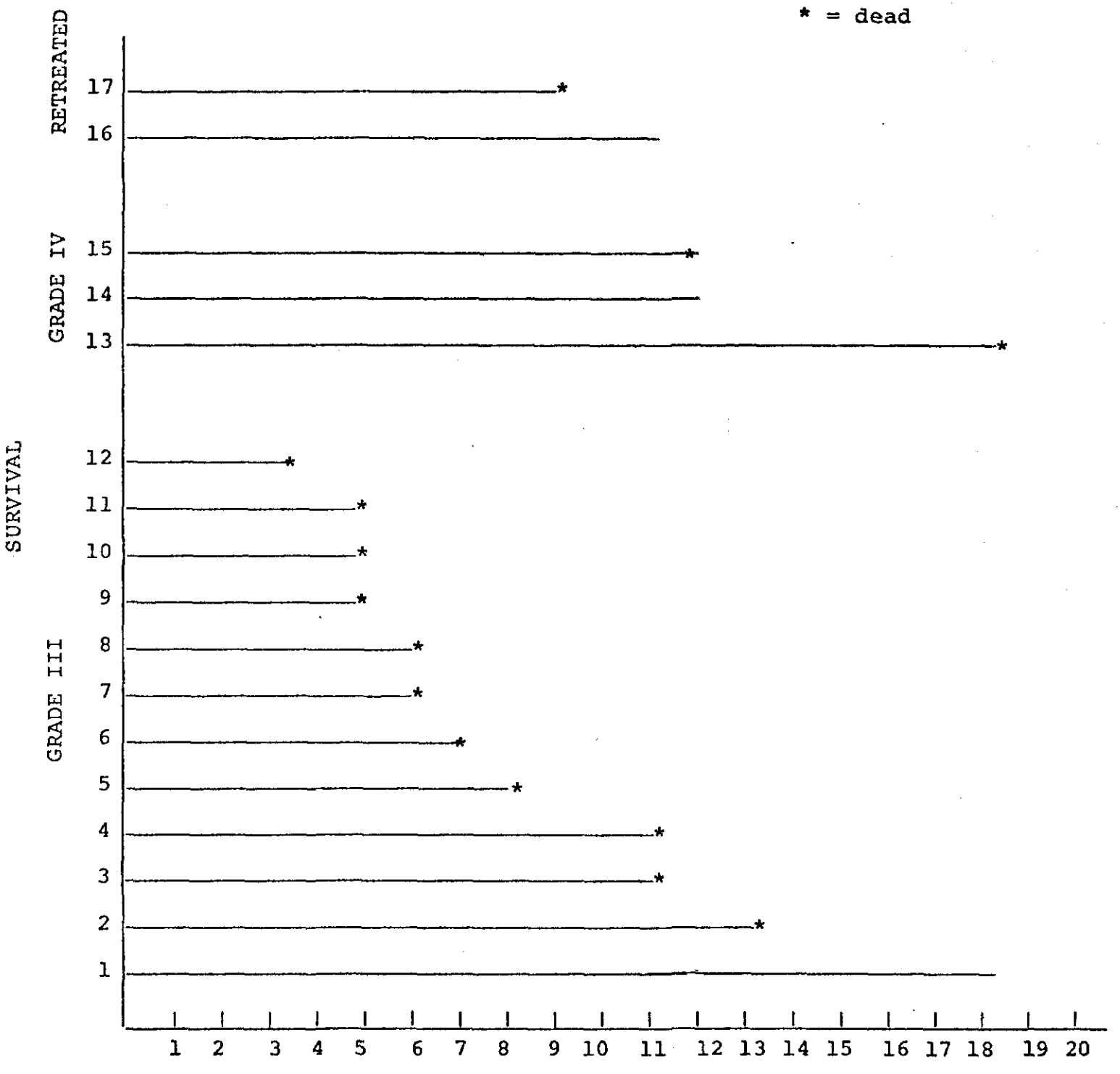
Retreated with neutrons after recurrence following photon irradiation

| | | | |
|---|---|---|---|
| 3 | 2 | 1 | 1 distant metastasis |

* American Joint Committee Staging System

Fig. 1

GLIOMAS




Grades III - IV are treated as Grade III

TABLE II



FLEXILAB NEUTRON DOSAGE OPTIONS (6 WEEKS' TREATMENT)

| FRACTIONS PER WEEK | 4 (Protocol) | 3 | 2 (Non-Protocol) | 1 |
|---|---|---|---|---|
| Nominal weeks treatment | 6 | 6 | 6 | 6 |
| Number of fractions - min. | 25 | 20 | 13 | 7 |
| max. | 27 | 21 | 14 | 8 |
| Actual treatment days - min. | 43 | 44 | 43 | 43 |
| max. | 47 | 48 | 49 | 50 |
| Dose Per Fraction | 80 | 100 | 150 | 250 |
| Total dose (rads) - min. | 2000 | 2000 | 1950 | 1750 |
| max. | 2160 | 2100 | 2100 | 2000 |
| Photon Equiv. (1900 ret) | 6500 | 6100 | 5600 | 4900 |
| Virtual RBE | 3.3 | 2.9 | 2.7 | 2.5 |
| Neutron boost after 4500 rads photons to give 7000 rad-equiv. | 10x80 = 800 | 8x100 = 800 | 5x150 = 750 | 3x250 = 750 |

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## CONCLUSIONS

It is too early to draw valid conclusions as a result of the Fermilab experience alone, but the modality can be evaluated in conjunction with observations from other centers as reported at the Hague meeting. Our experience appears to be consistent with conclusions presented by Jean Dutreix at that meeting. In summary, the data showed the results with brain tumors to be uniformly discouraging. Results with locally advanced epidermoid carcinomas were consistently superior with the neutron beam. Many reputedly radioresistent adenocarcinomas and sarcomas respond dramatically to neutron irradiation, although long term control and survival remains to be evaluated.