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CLINICAL EVALUATION OF NEUTRON BEAM THERAPY: CURRENT RESULTS AND PROSPECTS (1983)

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Neutron Beam: Results & Prospects, L. Cohen

ABSTRACT

Some 9,000 patients throughout the world have now been treated by some form of neutron beam therapy. These include patients with advanced non-resectable tumors in many different sites treated with a variety of neutron beam generators varying widely in beam energy. Protocols were largely non-randomized and included both mixed beam studies (neutrons + photons) and neutrons alone in varying doses.

In spite of wide variation in equipment, treatment technique and philosophy, some consistent trends have been identified: (1) in general the neutron results have been at least as good as those of the photon controls measured in terms of local control, although the incidence of significant side effects have been higher; (2) in none of the randomized studies carried out so far, largely comprising epidermoid carcinomas of the head and neck, has a clear survival advantage for neutrons over photon controls been demonstrated at a statistically significant level; (3) results with mixed beam studies have been uniformly equivocal, with marginally significant differences in favor of the experimental groups compared with the photon controls; (4) adenocarcinomas of the GI tract, including tumors of salivary gland, pancreas, stomach and bowel, appear to be responsive to high-LET radiations; (5) non-epidermoid, radioresistant tumors (sarcoma of bone and

soft tissue and melanoma) yield a consistantly high local control rate with neutron irradiation strikingly superior to those reported with photon therapy; (6) in the central nervous system both normal tissues and tumors appear to be exceptionally sensitive to neutron irradiation, therapeutic ratios are small, and the prospect of cure remains remote.

It is concluded that neutrons are efficacious for certain specific tumor types, but that essentially new study designs, based on non-randomized matched case comparisons, will be required to prove the merit of the new modality.

KEY WORDS: Neutrons, protocols, radioresistant tumors.

1. INTRODUCTION

The total number of patients reported to have been treated with neutrons throughout the world now exceeds 9000 (estimated for December, 1983). The Fermilab Neutron Therapy Facility, which started treating patients in September 1976, is the largest single contributor having accrued over 1300 patients in the past 7 years, representing 14% of the world total. This seems an appropriate time to evaluate our accumulated experience with neutron therapy and to determine, as far as possible, the most promising and productive areas of research for the immediate future as well as the probable long-term applications of neutron beam therapy in radiotherapeutic practice. This period is also a historical watershed in the high-LET program, which is now entering a phase where relatively high energy neutron beams, generated from clinically dedicated cyclotrons in hospitals, are coming into use in several countries. At the same time, new applications of radiotherapy for conditions previously believed to be radioresistant are becoming possible.

Up to now the majority of patients treated by us with neutrons have been those referred by radiation oncologists through established referral patterns and networks. Referrals, for the most part, have been late stage epidermoid carcinoma of the upper alimentary and air passages, the esophagus, lung and uterine

cervix. The rationale for this approach was that these advanced tumors contained a relatively resistant hypoxic cell moiety, which was expected to be more responsive to high-LET radiations. Less attention was paid to the intrinsically radioresistant tumor types, which are conventionally treated by surgery in the belief that radiation has no role to play in their management. Such patients are not normally seen by the practicing radiotherapist, and they are not readily accessed through conventional radiation therapy referral systems. Current studies now show that it is precisely these relatively radioresistant tumor types which are most responsive to neutron therapy, suggesting that future studies should be mainly directed towards these tumors.

It is a disconcerting fact that, in spite of the very large number of patients who have been treated with the new modality throughout the world, there is still no unequivocal convincing and independently corroborated proof of the superiority of neutrons over conventional irradiation in any of the groups studied. It is the object of this report to determine the reasons for this lack of success, and to identify any tactical errors in the research which may have been made in the past and which can be more clearly recognized in the light of current experience. Finally, we will propose new protocols and procedures for future investigation.

2. NEGATIVE OR EQUIVOCAL RESULTS

In evaluating a new modality, negative results (where the new technique failed to meet expectations) are just as important as successful studies. Together, they help clarify mechanisms and provide insights into the clinical significance of the results obtained. A number of studies, both at the Fermilab Neutron Therapy Facility and in other centers, have failed to demonstrate any real superiority of neutrons over standard radiation therapy, and consequently must be classified as essentially negative results. In order to establish the superiority of a new modality, it is necessary that local control and/or survival in patients so treated be higher than the corresponding figures with standard radiation, to such an extent that the differences are significant in both the statistical and the clinical sense.

2.1 Epidermoid Carcinoma of the Head and Neck. Several studies on the use of neutron beams for late stage (T_{2-4}, N_{1-3}) epidermoid carcinoma of head and neck have yielded either negative results or clinically insignificant equivocal results (a modest improvement in local control at a marginally significant level).

The results of the Hammersmith trial reported by Mary Catterall[1] showed a highly significant difference in favor of neutrons (76% control with neutrons compared with 19% with

photons), at the expense of a slightly higher incidence of significant side effects in the neutron group (Table 1). In the corroborative experiment at Edinburgh,[2] similar patients treated to essentially similar doses also yielded a high local control rate with neutrons but showed a similarly high success rate in the group treated with photons to biologically equivalent doses (similar complication rate). These results suggest that the Hammersmith experiment may have owed its significance to a slight but critical under-dosage in the photon series, and that the difference becomes much less striking when both arms are treated to full tolerance limits. One relatively "successful" randomized trial is that reported by Griffin, et al.[3], in which mixed-schedule (neutron + photon) irradiation of metastatic cervical adenopathy compared with photon-treated controls, showed significantly better results in the neutron treated group. Although the improvement in local control was statistically significant (p.=03), the clinical significance remains doubtful since survival was only marginally improved.

An RTOG trial of concomitant (mixed schedule) or sequential (neutron boost) protocols for epidermoid carcinoma of the head and neck has been completed, and although the final report has not been published, preliminary results suggest that the superiority of the neutron-containing mix will be marginal (local control rate less than 10% higher than that for the photon groups).[4] Epidermoid

cancer in other sites, notably the cervix, show similar trends in that results with neutrons, either used alone or in combination with photons, are little better than those obtained with photons alone.[5] A completely different situation is observed when nonepidermoid cancers of the head and neck are studied. These will be described below.

An analysis of the results of neutron and photon beam irradiation in epidermoid head and neck tumors treated at Fermilab showed both neutron and photon groups to have a steep dose-response function in which a critical trade-off between tumor control and normal tissue damage could be demonstrated. When the relative merits of the two modalities are compared in terms of the probability of uncomplicated control, both groups were essentially similar and no gain factor for neutrons could be demonstrated.[6]

In this study (Table 2), a comparison of normal tissue and tumor responses in patients treated with the high energy Fermilab neutron beam and conventional photons (^{60}Co and 4 MeV x-rays), yielded the following parameters. For neutrons, the median dose for significant radiation injury in the irradiated tissues was 31 ($\pm$2)Gy and the median dose for local control of the tumor was 26 ($\pm$2)Gy. The corresponding doses for photons were 90 ($\pm$4)Gy for normal tissue injury and 74 ($\pm$3)Gy for local control of the tumor. Therapeutic ratios are similar (about 1.2) in both groups.

Similarly, the RBE of neutrons relative to photons is about the same for normal tissue tolerance and for tumor control. Under these conditions, there is no demonstrable therapeutic gain factor for neutrons relative to photons. The overall uncomplicated local control rate was the same for both modalities (44%).

The absence of a demonstrable gain factor for neutron beam irradiation of epidermoid cancer suggests that the original premise, that hypoxia was an important consideration in determining radioresistance, is probably at fault. It now seems likely that redistribution and reoxygenation in the surviving cell populations during a fractionated course of radiation therapy effectively eliminates the radioresistant hypoxic subpopulation.[7] Thus, with conventionally fractionated treatments delivered over five to seven weeks, hypoxia is irrelevant and this rationale for the use of neutrons cannot be sustained. This might not be true with reduced fractionation, shortened courses of treatment, or non-epidermoid tumors.

2.2 Brain Tumors (Glioblastoma). Another area of essentially negative results is seen in the treatment of high-grade gliomas (glioblastoma). Since long-term control is exceedingly rare in this type of tumor, the efficacy of treatment is generally evaluated in terms of median survival times. Initial studies[1] indicated that neutrons in full dose did not extend survival

significantly but did cause widespread necrosis and often complete regression of the tumor (observed at autopsy). The RTOG study of mixed beam irradiation compared with photon controls in a randomized series in the United States also showed no difference in median survival between the two groups.[3]

A reduced fractionation pilot study, with and without the hypoxic cell radiosensitizer misonidazole, using neutrons alone in six large once weekly fractions of 3 Gy, has been completed at Fermilab.[8] The main objective was to determine tolerance in terms of acute and late effects as well as to estimate tumor clearance rates and survival rates. The median survival for the whole group was 12.5 months and 25% were alive at 18 months with some neurological compromise. Autopsies showed both residual tumor and radionecrosis in all cases. Comparison of the two study groups showed no differences in response. As the study matures it appears unlikely that there will be any long-term survivors (beyond three years) in this series.

2.3 Intrathoracic Tumors. A third "negative" group was provided by a small number of intrathoracic epidermoid carcinomas, treated with either neutrons alone or mixed modality procedures. These comprise 39 carcinomas of the esophagus[9] and 33 carcinomas of the lung (unpublished data, Fermilab Neutron Therapy Facility). The results shown (Table 3) do not indicate any striking improvement in response which can be attributed to the neutrons.

3. POSITIVE RESULTS WITH NON-EPIDERMOID TUMORS

In contrast to our results with epidermoid cancer, in which no superiority of neutrons over photons could be demonstrated, either in terms of local control of the disease or in overall survival, several other tumors have shown a positive response.

International experience with neutron therapy for reputedly radioresistant non-epidermoid tumors in various sites is summarized in Tables 4 and 5. In general, these were non-randomized studies because it was considered ethically unacceptable to use a photon control arm in many situations where the response to photons was believed to be poor. Results are strikingly consistent in spite of widely differing treatment philosophies, different patient populations and a wide range in beam energies.

3.1 Non-Epidermoid Carcinoma of Head and Neck. In salivary gland tumors, all studied cases being advanced, nonresectable, and usually large in volume, 28 out of 39 patients treated with neutrons alone at Fermilab were controlled (72%) as were 11 out of 17 patients treated with mixed modalities (65%). Corroborative studies in other centers showed a consistent 74% control rate for neutrons (Table 5), compared with no more than 50% for photon controls.[10]

In a comparison of results for epidermoid and non-epidermoid carcinomas of the head and neck at Fermilab, Kurup, et al.,[11] demonstrated markedly improved local control in the non-epidermoid tumors. This series of patients comprised locally advanced, nonresectable, adenocarcinomas, adenocystic tumors, and mucoepidermoid carcinomas affecting both the major and minor salivary glands, common sites for minor salivary glands (buccal mucosa, soft palate, and antrum), and other sites including the orbit. The most significant factor determining the outcome in this series of patients is the histological type. For epidermoid carcinoma long-term local control was achieved in 17/35 patients (49%); compared with the salivary-type tumors in which the local control rate was 28/39 (72%). Disease-free survival analysis also shows a survival advantage in non-epidermoid lesions treated with neutrons. It is concluded that neutron beam therapy may well be the treatment of choice for non-resectable or recurrent, non-epidermoid cancers of the head and neck. These nonepidermoid tumors of the head and neck were, apart from the histology, very similar in regard to stage and clinical characteristics to the analogous series of epidermoid cancers.

3.2 Adenocarcinoma. Adenocarcinomas in other sites appear to be relatively responsive to neutron irradiation. In pancreatic cancer,[12] for example, although neutron irradiation showed no significant improvement in survival, the local response was

remarkably different from that observed with conventional irradiation. In a series of 83 patients with carcinoma of the pancreas treated at Fermilab the median survival was 8.5 months, failure being attributed mainly to metastatic dissemination and occasionally to complications of treatment. In the autopsied series (26 patients), the neutron-irradiated pancreas showed massive fibrosis in all cases, with sparsely distributed foci of persistent cancer. This response appears to be characteristic of high-LET radiation[13]; it is apparently less marked when photons or other low-LET particle beams are applied in biologically equivalent doses.

Cancer of the rectum and sigmoid colon represents another area where the responsiveness of adenocarcinomas of the human G.I. tract can be observed. In a series of 25 patients treated in Amsterdam (Table 5) local control was achieved in 13 cases (53%). In another 25 patients treated with photons to maximum tolerated doses, all tumors persisted (local control 0/25).[14]

3.3 Sarcomas of Bone and Soft Tissue. Twenty-five patients were treated for bone sarcomas and 26 for sarcoma of soft tissues at Fermilab.[15] The response was evaluated after follow-up periods from two to six years. The histological subtypes and the corresponding local control rates are listed in Table 6 together with data on the size and location of the tumors when treatment

commenced. The overall local control rate for sarcomas of bone and soft tissue is about the same and approximately equal to 50%. This is slightly lower than the average for collected data on these two tumor types reported from various centers (Table 5), which is approximately 60%. The difference can probably be accounted for by the exceptionally advanced tumors referred for treatment to the Fermilab Neutron Therapy Facility.

The 60% local control rate for neutron irradiation of sarcomas of bone and soft tissue may be compared with historical photon controls.[16,17] A comparable control series reported by DeMoor[18] showed local tumor ablation in 6 out of 11 post-irradiation amputations for bone sarcomas treated with doses of 70-80 Gy. Suit[19] and Tepper[20] have shown a small proportion local controls in soft tissue sarcomas treated with maximal doses of photons.

4. TACTICAL PROBLEMS

Existing protocols in the United States are based upon established referral patterns of patient management. Practicing oncologists have already defined those tumor types which are best treated by radiation, surgery, chemotherapy, or various combined modalities. This determination has been based on the results obtained with conventional radiation. Testing neutrons in the

context of patients referred for radiotherapy clearly excludes precisely those cases in which the new modality could have its greatest impact, namely, patients presently considered unsuitable for radiation therapy.

In several studies "mixed-beam" irradiation was used in preference to neutrons alone for comparison with the photon-treated controls. Reasons included better dose distribution and treatment plans (where neutron beam energies were inadequate), possible biological advantages associated with the interaction between the two modalities, and encouraging referrals by participating radiotherapists. Responses may have been partially vitiated by diluting the more effective modality, and additional errors may have been introduced by combining the treatment plans for the two modalities, each with its individual constraints and limitations. With the exception of the single report on metastatic cervical adenopathy[3] results of all mixed beam studies reported so far have been equivocal.

Where randomized studies entail comparison between two modalities, it is assumed implicitly that each modality is applied in equivalent doses. In practice, late effects in normal tissues have invariably been somewhat more severe in the neutron-containing groups of all randomized studies. It is then difficult, if not impossible, to attribute any observed

differences in response rates to the modality chosen rather than to errors in equivalent doses. In retrospect the only effective method for deriving the required information would have been a four-point assay (two neutron doses and two photon doses) permitting RBE's and control probabilities to be determined.

A real advantage of one modality over the other would then be recognized (a) if the new modality led to a significantly higher probability of uncomplicated control (tumor cure without unacceptable normal tissue damage); or (b) if the estimated RBE for tumor control were significantly greater than the estimated RBE for normal tissue damage.

5. DISCUSSION

The use of neutrons and heavy charged particles in radiation oncology necessitates the introduction of costly new technology into the field of medical care. The cost and effort of such developments can be justified if cancer cure rates or the quality and productivity of life can be improved substantially. The new modality should be looked upon as an agent for curing cancers which are not amenable to conventional therapy, or for providing substantially better end results in terms of functional capacity than any available alternative procedures. The impact of the new modality should be a clinically significant advance, not merely a

statistically significant gain in the local control of cancers which would normally be treated by radiation.

In many situations radiation therapy has the advantage over radical surgery of ablating the tumor without significant impairment of structure and function. Where radiation therapy is ineffective, in relatively radioresistant tumor types, extensive resections remain the only effective management. Questions which need to be addressed seriously are: can high-LET radiations cure radioresistant tumor types thus avoiding mutilating surgery in technically resectable cases? Can high-LET radiation yield some prospect of cure in inoperable cases? From this point of view, all the results reported so far have been inconclusive.

Reasons for these inconclusive results include the choice of epidermoid carcinoma as a subject for study, and failure to recognize that at least two dose levels need to be studied with each modality if therapeutic gain factors are to be identified. Also, the use of mixed modalities, neutrons and photons in some convenient concomitant or sequential combination, may have diluted the effect of the high-LET beam, and rendered comparison between the experimental and control arms more difficult.

It is probable that the relative radioresistance of large epidermoid cancers is not due to hypoxia or to intrinsic cellular radioresistance, but rather to the relatively large doses required to ablate the correspondingly large cell populations involved. If a significant hypoxic cell component exists in these tumors, its effect is largely offset by the relatively efficient reoxygenation process which also occurs.[7] With the modest change in OER effected by neutrons the gain is apparently too small to be measurable. The implications are that if the photon dose were sufficiently high, possibly 80 Gy, local control with photons would be equivalent to that obtained with the maximal tolerated doses of neutrons. These dose levels are expected to yield equivalent complication rates, implying that the relative effectiveness of the two modalities for both tumor control and normal tissue reactions are about the same.

On the other hand, with slowly cycling tumors, the neutron RBE has been shown to increase progressively as the volume doubling time is prolonged[21] These tumors are commonly "radioresistant" (to photons), probably by virtue of the large proportion of relatively insensitive non-cycling cells, but since the response of cells to high-LET radiation is virtually independent of their position in the mitotic cycle, such tumors would be expected to be more readily controlled by neutrons. This is borne out by the results of neutron beam irradiation in

non-epidermoid tumors (adenocarcinoma, sarcomas of bone and soft tissue, other "radioresistant" tumors) which are markedly different from those observed with epidermoid carcinoma. The pilot studies of neutron beam irradiation for advanced, non-resectable tumors in these categories show long-term local control rates of the order of 70%. A striking feature of these results, based on a total of some 600 patients in these categories treated in various centers, is the consistency of the observed response rates in various patient populations, beam energies and treatment conditions.

Since the patients studied have been selected because of their advanced stage and unsuitability for conventional treatment, they are likely to represent the worse cases (patients with the poorest prospect of success), which lends further credence to the efficacy of neutrons in these situations. However, there are no controlled randomized studies for this category of tumors, and the statistical validity of the results observed can consequently be challenged. The key question, would these patients have done equally well with equivalent doses of photon irradiation, remains to be answered. Since past radiotherapeutic experience suggests that the response of these tumors to photon irradiation, even in maximally tolerated doses, is very poor, we are faced with a serious ethical dilemma in resolving this question. In order to prove the efficacy of neutrons in "radioresistant" tumors, it is

necessary to choose those tumor types in which the difference in response-rate with neutrons compared to photon controls is expected to be large. On the other hand, the classical randomized clinical trial can be justified on ethical grounds only if expected differences are small and consequently the superiority of one modality over another is uncertain. Where large differences are anticipated, the classical randomized trial is unacceptable.

Of the six tumor types listed in Table 5, only one, namely salivary gland tumors, has been subject of a randomized trial.[22] Even in this category, serious questions in regard to the ethics of such a trial have been raised, and some dissenting radiation oncologists have refused to participate (personal communication, M. Catterall). It will probably not be possible to institute randomized studies in the remaining five categories. Since these categories are almost certain to be among the major indications for high-LET radiations in cancer management, this question will become a serious issue in designing future studies in the high-LET program.

Clearly, two distinct strategies will need to be implemented in future programs. These will comprise, first, a strategy for evaluating neutron beam therapy compared with best current photon treatment for patients normally referred for conventional radiotherapy, and in whom the prognosis is believed to be

relatively poor. A second and different strategy will be required for patients with tumors classified as radioresistant, who are not normally referred for radiation therapy, but in whom neutron therapy may prove to be helpful in curing the tumor without recourse to extensive surgery or in controlling the disease when the tumor is non-resectable. In the former instance, comparing neutron and photon beams, the randomized clinical trial in the form of the four-point assay to be described is probably appropriate. In the latter case randomization is probably impracticable and alternative methods of evaluation will have to be considered. Two approaches are currently being explored at Fermilab.

(1) Randomized studies will be used for tumors in which small differences are anticipated. In this situation an initial determination of the tolerance limit is made, either by a dose-searching escalation procedure to determine the acute tolerance limit in an initial pilot study or by review of patients treated previously in the same anatomical region to determine the incidence of significant side effects in relation to dosage delivered. Two treatment arms are then chosen, one above and one below the assumed tolerance dose. Two corresponding photon treatment arms are similarly selected. These four treatments then provide data from which the necessary dose effect relationships, probabilities of uncomplicated control, and the gain factor if any

of neutrons versus photons can be determined.

The steep dose-effect functions observed[6] suggest that a narrow range of doses, possibly differences by no more than 10%, would be sufficient to determine the median position and slope of the function. These estimates could be derived by linear interpolation, or more realistically fitting an appropriate function (logistic or probit) to the data.

(2) For non-randomized studies where the expected difference may be large, the tolerance dose is determined as described and two neutron arms are selected for study. All patients referred are randomized between these two values. At the same time matched photon controls will be treated at another institution, chosen for its interest in treating the tumors concerned radically and reporting better-than-average results. Matching will be achieved by a common review in both centers of the pathology, staging, and measurement of exact tumor volumes. The feasibility of this approach remains to be evaluated.

6. CONCLUSIONS

The primary object of the high-LET research program is to determine whether an appropriate course of particle therapy would yield a better clinical result than best current practice

available with conventional beams. In this context "better result" means a significantly higher cure-rate with no concurrent increase in complications, or a similar cure-rate with significantly fewer complications. Here "significant" implies not only statistical significance in the strict sense but also clinical significance, that is a sufficiently large difference to offset the increased costs (in money, time, inconvenience, and patient discomfiture) of the new modality. A significantly better treatment is believed to be one which yields an improvement of at least ten percentage points in uncomplicated control or survival rates, with a probability of less than 0.05 that the difference has occured by chance. The comparison also implies that both modalities were used optimally, with the technical variables (dose, fractions and time) most appropriate for each modality.

A wide variety of tumor types, reputed to be "radioresistant", appear to be amenable to complete local ablation by neutrons without significant side effects. These tumors have hitherto been treated exclusively by surgery or by mixed modality procedures (pre-operative irradiation and wide resection).

Neutron beam therapy could provide equally effective local control while avoiding the functional and cosmetic disturbance of cancer surgery. Patients suitable for this approach are those with late stage non-epidermoid cancers of the head and neck,

advanced salivary gland tumors, sarcomas of bone and of soft tissue, non-resectable melanoma, and pelvic tumors (bladder, prostate and rectosigmoid).

The impact of the new modality is fourfold: (1) neutrons expand the scope of radiation therapy to include intrinsically radioresistant tumors hitherto considered unsuitable for irradiation; (2) where tumor ablation can be accomplished by irradiation alone, new procedures for conservative or corrective surgery become feasible; (3) with improved control of local disease, neutrons expand the role of elective chemotherapy for the prevention or retardation of metastatic growth; and (4) neutrons expand the range of options available to the cancer patient who may wish to consider conservative treatment with the new modality as a possible alternative to radical surgery.

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6. Sarcoma of Bone and Soft-Tissue, Response to Neutrons. (Fermilab 1976-1981).

Table 1

Local Control in Epidermoid Carcinoma of the Head and Neck

Experience as of February 1982

	PHOTONS				NEUTRONS			
	Treated	Contr.	Compl.	PUC*	Treated	Contr.	Compl.	PUC*
Hammersmith[1]	63	12(19%)	3(5%)	18%	70	53(76%)	12(17%)	63%
EORTC**[13]	95	41(43%)	8(8%)	40%	100	48(48%)	16(16%)	40%
Houston[31]	41	18(44%)	3(7%)	41%	49	3(47%)	10(20%)	37%
Fermilab[5]	73	32(44%)	4(5%)	41%	51	28(55%)	11(22%)	43%
T AL	272	103(38%)	18(7%)	35%	270	152(56%)	49(18%)	46%

*PUC (Percent Uncompl. Contr.) = (Control Rate)x(1-Complication Rate).

**EORTC - European Organization of Radiation Therapy Centers.

Table 2

Local Control And Complication Rates of Epidermoid Carcinomas
As a Function of Target Absorbed Dose
For (a) Neutrons and (b) Photons.
Fermilab Data[2]

(a) NEUTRONS

DOSE(Gy)	Patients	Controls	Compl.	RATES Cure%(*)	RATES Compl.%(*)
≤19	2	0	0	17(±11)	0
20-21	10	2	0		
22-23	6	3	1	50(±13)	21(±11)
24-25	8	4	2		
26-27	16	8	5	53(±12)	29(±12)
≥28	1	1	0		
TOTAL	43	18	8	42(±7)	19(±6)

Medians: Control 26(±2)Gy; Complications 31(±2)Gy
(*)Standard errors of ratios.

(b) PHOTONS

DOSE(Gy)	Patients	Controls	Compl.	RATES Cure%(*)	RATES Compl.%(*)
≤62	5	0	0	0	0
63-67	3	0	0		
68-72	42	19	1	45(±8)	2(±2)
73-77	15	8	2	57(±10)	13(±7)
≥78	8	5	1		
TOTAL	73	32	4	44(±6)	5(±3)

Medians: Control 74(±3)Gy; Complications 90(±4)Gy
(*)Standard errors of ratios.

Table 3

Intrathoracic Tumors

The Fermilab Experience 1976-1980

(a) LUNG

	Number	Local Control	Complications	Number Alive	Median Survival (Months)
Neutrons Only	37	6	6	8	8.0
Mixed Beam	7	1	3	0	9.1
TOTAL	44	7	9	8	8.5

(b) ESOPHAGUS

	Number	Local Control	Complications	Number Alive	Median Survival (Months)
Neutrons Only	9	3	4	0	9.0
Mixed Beam	30	6	15	7	10.9
TOTAL	39	9	19	7	10.0

Table 4

Epidermoid and Non-Epidermoid Carcinomas of the Head and Neck

Comparative Response to Neutrons

The Fermilab Experience, 1976-1980

Histol.	Epidermoid Carcinoma	Non-Epidermoid Carcinoma	
Prev. Treatment		Major Salivary Gland	Other
None	13/26	4/6	5/9
Surgery	4/9	10/14	9/10
TOTAL	17/35	14/20	14/19
Percent	49%	70%	74%

Table 5

Long-Term Control in 629 Non-Resectable Radioresistant Tumors Treated By Neutrons - International Experience, Dec. 1982.

TUMOR TYPE	FACILITY	TREATED	CONTROLLED	
1) SALIVARY TUMORS	Hammersmith (1)	40	30	
	Amsterdam (23)	30	22	
	Seattle (24)	11	7	
	RTOG (23)	31	25	
	Fermilab (25)	39	28	
	TOTAL	151	112	(74%)
2) SARCOMA OF BONE	MANTA (24)	7	6	
	CHIBA [Japan](26)	18	15	
	Essen (23)	24	12	
	Fermilab (15)	25	11	
	TOTAL	74	44	(59%)
3) SOFT TISSUE SARCOMA	Houston (27)	29	20	
	Hammersmith (1)	28	23	
	Amsterdam (24)	13	8	
	Hamburg-Eppendorf (28)	24	20	
	MANTA (24)	7	4	
	CHIBA (26)	12	7	
	EORTC [Europe](23)	189	108	
	Fermilab (15)	26	13	
	TOTAL	328	203	(62%)
4) MELANOMA	CHIBA (26)	14	12	
	Fermilab (a)	7	3	
	TOTAL	21	15	(71%)
5) RECTO-SIGMOID CANCER	Amsterdam (14)	25	13	(52%)
6) BLADDER CANCER	Amsterdam (14)	22	10	
	Fermilab (a)	8	5	
	TOTAL	30	15	(50%)

(a) Unpublished data.

Table 6

Sarcoma of Bone and Soft-Tissue

Response to Neutrons.

The Fermilab Experience 1976-1981

		SIZE		SITE			RESULTS	
PATHOLOGY	NUMBER	<5 cm	>5 cm	Head	Trunk	Limb	ALIVE(%)	CONTROL(%
BONE:								
Osteosarcoma	9	3	6	4	4	1	1 (11)	2 (22)
Chondrosarcoma	16	9	7	6	9	1	9 (56)	9 (56)
TOTAL	25	12	13	10	13	2	10 (40)	11 (44)
SOFT-TISSUE:								
Liposarcoma	7	2	5	1	4	2	4 (57)	5 (71
Fibrosarcoma	8	4	4	1	5	2	1 (13)	3 (38)
Leiomyosarcoma	5	3	2	1	4	0	0 (0)	1 (20)
Schwannoma	3	0	3	0	1	2	3 (100)	3 (100)
Synovioma	3	2	1	0	1	2	0 (0)	1 (33)
TOTAL	26	11	15	3	15	8	8 (31)	13 (50)
ALL SARCOMAS:	51	23	28	13	28	10	218(35)	24 (47)