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NEUTRON BEAM THERAPY: NORMAL TISSUE TOLERANCE LIMITS.

Cohen, L., Awschalom, M., Mansell, J., Hendrickson, F.,
Rosenberg, I., Ten Haken, R. K.
Fermilab Neutron Therapy Facility, Batavia, Illinois

Hussey, D., etc.
M. D. Anderson Hospital, Houston, Texas

ABSTRACT

Normal tissue reactions were studied in 138 patients irradiated for tumors of the head and neck. Of these, 24 were treated with d(50)Be neutrons in Houston (TAMVEC), 49 received p(66)Be(49) neutrons in Chicago (Fermilab) and 65 patients in the Chicago region were assigned standard photon beam therapy.

Severe reactions (marked fibrosis, mucosal ulceration or soft tissue necrosis) were observed in 30 patients. Median doses (yielding 50% incidence of late reactions) were 23 Gy, 28 Gy and 85 Gy respectively in the 3 groups studied. The corresponding tolerance limits (associated with a 5% risk of injury) were 18, 21 and 63 Gy respectively.

Equivalency factors for the neutron beams were 3.7 (±0.2) for TAMVEC and 3.0 (±0.2) for Fermilab. TDF values were calculated for all treatments using appropriately modified parameters for the neutron beams. A common median level (50% risk) was found around TDF = 126 (±2). The 5% risk level was TDF = 98 (±2) calculated on the same basis.

Keywords: Tissue tolerance, neutrons, RBE, TDF.

1 INTRODUCTION

Effective treatment of deep seated tumors by neutrons requires penetrating beams generated by relatively high energy particle accelerators with peak energies of 40 MeV or higher. Up to the present time clinical experience is largely founded on data from low energy cyclotrons operating at about 15 to 22 MeV and providing neutron beams suitable only for accessible or superficially placed lesions. Neutron beams produced by the high energy processes differ markedly in both the mean neutron energy and the spectral distribution of energies from those produced by the low energy deuteron-beryllium reaction. In the two situations, the irradiated tissues will have substantially different distributions of dose in LET (linear energy transfer), with associated differences in RBE (relative biological effectiveness). The clinical response or the radiosensitivity of specific tissues is also likely to be different with different beams.

The high energy beam produced by the p(66)Be(49) process has been extensively studied at Fermilab in both its physical and biological aspects.[1] Tentative estimates of RBE's and clinical equivalency factors have been determined.[3] The next generation of hospital based neutron therapy installations in the U. S. and abroad are designed to use the high energy proton-beryllium reaction (there are significant technical and dosimetric advantages in using this reaction, rather than the deuteron-beryllium process, at high energies). The beams produced will consequently have LET distributions, RBE values and tissue tolerances considerably different from previously established clinical experience, and probably closer to those observed with the Fermilab fast neutron beam.

The object of this report is to establish normal tissue tolerance limits for fractionated therapy over 6 weeks with high energy neutrons. Responses with the Fermilab [p(66)Be(49)] beam are compared with corresponding data for the TAMVEC [d(50)Be] beam. The relevant tolerances are expressed in terms of target absorbed doses at the 2 centers, and the appropriate time dose factor (TDF) formulation is determined.

2 MATERIALS AND METHODS.

The study comprises 24 patients treated with the d(50)Be neutron beam at TAMVEC (Table 2) and 51 patients treated with p(66)Be(49) neutron beam at Fermilab (Table 3), during the period 1975 to 1980. All cases reported have been followed for between 2 and 5 years after treatment. Acute skin and mucosal reactions were annotated and any late effects or radiation induced injuries observed were graded according to the RTOG-EORTC convention (Table 1). The highest grade scored at any time during the follow-up period was tabulated for analysis. For comparison a third group of 65 patients treated with photons (4 MeV or ^{60}Co treatments taken from the control arm of the randomized head and neck study) were analysed using the same criteria (Table 4).

3 RESULTS

The risk of radiation injury is assessed in terms of the frequency of "severe" reactions (grade III in the RTOG-EORTC convention) at various dose levels (Table 5). Reactions of this severity were readily graded without equivocation. They would normally be classified as complications of treatment, and include marked fibrosis, persistent ulceration or soft tissue necrosis within the treated volume.

Neutron doses ranged from 18 to 27 Gy and were grouped as shown in Table 5. The number of patients and the number showing reactions of grade III or higher is shown in Table 5a for each dosage group at both the TAMVEC and Fermilab facilities. The corresponding numbers for photons in the 50-80 Gy dosage range are given in Table 5b. The ratios (reactors:total) are plotted in Figure 1 and evaluated by probit analysis. This analysis gave median values (μ or ED-50) of 23 (±1) Gy for TAMVEC neutrons, 28 (±1) Gy for Fermilab neutrons, and 85 (±3) Gy for the photon controls. The slope of the dose response lines (σ, or sample standard deviations) are 5, 3 and 13 respectively. The coeffecient of variation (σ/μ) is 12% and 18% respectively for the TAMVEC and Fermilab studies and 17% for photons. The effectiveness ratio calculated for the 2 neutron beams is 0.82 (±.05), suggesting that the TAMVEC beam may have an RBE of some 20% greater than the Fermilab beam.

Since the median doses for the neutron beams are essentially similar, the TDF formulation using the standard parameters for photons and coefficients derived for Fermilab neutrons,[2] should be applicable to the whole data set. Table 6 shows observed reaction rates in relation to calculated TDF values. Probit analysis yielded a common median value of 126 (±2) and a standard deviation of 17. A TDF of 98 then corresponds to the 5% risk level. Expected frequencies of moderate and severe normal tissue reactions for various estimated TDF levels are shown in Fig. 3.

4 DISCUSSION

The relative biological effectiveness of the two beams in the study apparently differed by a factor between 0.8 and 0.9. Previous radiobiological studies[4] at the two facilities, using mammalian cell cultures and mouse skin irradiation, failed to demonstrate significant differences between the beams. However, an analogous study was reported by Van Dam and Wambersie[6] comparing the effects of p(75)Be and d(50)Be neutrons in a laboratory system (V.faba). These two beams would have neutron energy spectra quite similar to those used in the present clinical study. The relative effectiveness observed was of the order of 0.85 ($\pm$0.1) which is clearly compatible with our observations.

The effectiveness of neutrons relative to photons in the clinical context is best expressed by an "equivalency factor" (in preference to RBE which is dose dependent). The equivalency factor is defined as the RBE determined for neutrons relative to conventionally fractionated photons.[5]

Results of this study suggest that the equivalency factor for high-energy neutron beams was between 3.0 $\pm$0.2 (Fermilab) and 3.7 $\pm$0.2 (TAMVEC) if median (50%) values for the risk of radiation injury are compared. Since the neutron and photon dose-effect levels in Fig. 1 are not exactly parallel, the equivalency factor could be different for lower risk levels. At the 5% level (μ-1.65σ), the corresponding values are 3.0 and 3.8 respectively.

The "tolerance limit", associated with a 5% risk of severe reactions is roughly 63 Gy of appropriately fractionated photons (Fig. 1) which corresponds to neutron doses of 18Gy (TAMVEC) and 21 Gy (Fermilab). A photon dose of 63 Gy delivered in 35 fractions over 47 days yields a calculated NSD of 1760 ret and a TDF of 98. Similarly a neutron dose of 21 Gy given in 14 fractions over 45 days (twice a week) yields a calculated TDF of 96. The normalization constant (K in the neutron TDF formula[Ref]) used for this estimate was 0.022 based on Fermilab data. The possible difference in effectiveness of the two beams suggests that this factor could be as high as 0.026 for the d(50)Be neutron beam at TAMVEC. A working value of .024 is probably appropriate for TDF calculation in high-energy neutron therapy. The neutron TDF equation (for D Gy in N fractions over T days) then reads

$$TDF = .024 \times N \times (100\ D/N)^{1.176} \times (T/N)^{-0.129}$$

5 CONCLUSIONS

Reactions in patients treated with two neutron beams, one generated by 66 MeV protons on a thin (49 MeV) beryllium target and another by 50 MeV deuterons on a relatively thick target, were compared. The p(66)Be(49) beam required a significantly higher target absorbed dose in order to produce the same degree of damage to normal tissues. The RBE values for the two beams relative to photons were 3.0 ($\pm$0.2) and 3.7 ($\pm$0.2) respectively.

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Table 1

Late Radiation Morbidity Scoring Scheme
(From RTOG/EORTC Report)

SCORE	GRADE	SKIN	MUCOUS MEMBRANE	CONNECTIVE TISSUE
1	Mild	Some atrophy, pigmentation, hair loss.	Some atrophy, dryness, loss of taste.	Some induration and fat loss.
2	Moderate	Patchy atrophy, depigmentation, telangiectasia.	Atrophy, telangiectasia, xerostomia, dysphagia.	Asymptomatic fibrosis.
3	Severe	Gross telangiectasia superficial ulceration.	Marked atrophy and telangiectasia, superficial. ulceration.	Severe induration and contracture.
4	Life threatening	Persistent or deep ulceration.	Persistent or deep ulceration.	Necrosis.
5	Lethal	Death directly attributable to radiation effects.		

Table 2

Normal Tissue Reactions - Head and Neck
Neutrons (24 patients) - TAMVEC SERIES

No.	DOSE (Gy)	FRACTIONS	TIME (DAYS)	TDF	SCORE
1	16.7	8	26	88	1
2	17.3	8	26	92	1
3	17.5	5	15	102	1
4	19.2	12	48	95	1
5	19.4	12	51	95	1
6	19.9	12	43	100	1
7	20.0	14	50	98	1
8	20.0	12	47	99	1
9	20.5	13	43	103	1
10	20.7	14	53	101	1
11	20.7	13	43	104	1
12	20.8	13	57	102	1
13	20.8	13	43	105	1
14	21.0	13	43	106	3
15	21.3	12	40	109	3
16	21.4	12	43	109	1
17	21.6	12	43	110	3
18	21.7	18	50	106	1
19	22.0	14	47	110	1
20	22.1	13	43	112	1
21	23.6	14	47	120	3
22	23.7	14	47	120	3
23	23.8	12	43	123	3
24	24.2	14	47	123	3

Table 3.

Neutrons (51 patients) - FERMILAB.

SERIAL	DOSE (Gy)	FRACTIONS	TIME (DAYS)	TDF	SCORE
77075	20.0	20	47	86	1
77045	21.0	14	64	88	1
77117	21.0	21	60	87	1
77124	21.0	14	65	88	2
77031	21.0	7	55	94	2
77090	21.0	14	36	95	2
77158	21.0	10	29	104	
80054	21.0	14	47	92	1
80235	21.0	8	29	101	1
80274	21.0	14	50	92	1
78250	21.6	18	39	96	1
76019	22.0	22	56	93	1
76023	22.0	22	56	93	2
78091	22.0	10	31	104	2
80003	22.1	14	47	98	2
77118	22.4	28	55	95	3*
80228	22.7	12	37	105	1
76021	23.0	23	57	98	1
76022	23.0	23	60	97	4*
80222	23.3	21	85	95	2
78075	24.0	12	44	110	2
78079	24.0	21	52	104	2
80089	24.0	20	46	106	3*
80260	24.0	22	61	102	1
78133	24.1	14	47	109	1
80190	24.6	13	47	111	1
80214	25.0	15	50	112	2
79009	25.2	14	46	115	3*
79046	25.6	14	51	115	5*
79038	25.6	20	63	111	2
80083	25.8	16	50	116	1
79032	26.4	18	55	118	2
79044	26.4	20	48	119	2
79068	26.4	12	44	124	2
79101	26.7	12	39	126	5*
80006	26.7	16	53	120	2
80074	26.7	15	50	121	1
80017	26.7	15	47	122	3*
80025	26.7	15	48	122	2
80029	26.7	16	56	119	2
80099	26.7	20	53	118	3*
80134	26.7	15	67	119	2
80136	26.7	15	51	120	1

SERIAL	DOSE (Gy)	FRACTIONS	TIME (DAYS)	TDF	SCORE
80187	26.7	15	55	119	2
80192	26.7	15	49	121	3*
80220	16.7	16	49	121	4*
80025	26.8	15	48	122	2
80075	26.9	16	62	118	3*
79073	27.0	20	50	120	3*
79222	27.1	17	43	125	2
80068	27.1	19	73	114	2

Table 4

Photons (65 patients) - FERMILAB.

SERIAL	DOSE (Gy)	FRACTIONS	TIME (DAYS)	TDF	SCORE
80190	55.0	25	57	87	1
80211	60.0	31	56	93	1
80047	61.2	34	45	96	1
78247	62.0	30	46	102	3
80038	65.9	40	76	92	1
77109	66.0	33	60	103	1
79166	68.0	34	59	107	2
80217	68.0	38	71	100	1
80026	68.5	38	52	107	1
79184	68.7	37	55	107	2
79090	68.8	36	62	106	1
79148	69.5	36	56	110	2
80245	69.8	33	37	122	2
77095	70.0	et	49	115	1
78014	70.0	38	58	109	1
78043	70.0	35	74	107	1
78055	70.0	35	51	114	2
78058	70.0	35	60	111	2
78104	70.0	35	50	114	3
78111	70.0	35	46	116	1
78198	70.0	35	66	109	2
78251	70.0	39	81	107	1
79042	70.0	35	50?	114	1
70025	70.0	35	64	110	2
79108	70.0	39	63	106	3
79128	70.0	35	64	110	2
80021	70.0	35	85	104	3
80063	70.0	35	48	115	2
80133	70.0	35	50	114	2
80196	70.0	36	87	103	1
80205	70.0	38	56	109	1
80256	70.0	39	68	104	2
80257	70.0	35	50	114	1
80149	70.1	39	62	106	2
79098	70.2	39	83	101	1
79156	70.2	39	52	109	2
80027	70.2	41	59	105	1
80247	70.2	39	60	107	1
79072	70.4	38	57	108	2
79107	70.4	38	62	108	2
80055	70.8	37	90	103	1
78202	71.0	38	60	110	2

SERIAL	DOSE (Gy)	FRACTIONS	TIME (DAYS)	TDF	SCORE
80159	71.0	35	54	115	2
78203	71.6	38	60	111	2
79070	72.4	38	61	113	3
79149	72.9	39	65	112	3
79040	73.4	38	75	111	2
79012	73.5	33	60	122	2
79014	73.5	30	61	126	2
78013	74.0	37	62	118	2
78026	74.0	48	60	107	1
78060	74.0	37	58	119	2
78112	74.0	38	64	116	3
78201	74.0	37	63	117	2
79061	74.0	37	59	119	1
79134	74.4	40	57	117	2
79216	75.0	42	67	113	1
79066	75.3	43	61	115	1
78119	75.5	37	63	121	3
79196	76.0	38	76	117	2
79051	78.0	38	58	128	1
78217	79.4	36	63	132	3
78084	80.0	40	66	127	3
80223	85.0	50	89	117	3
80224	90.0	50	86	135	2

Table 5

Incidence of Severe Normal Tissue Reactions

(a) Neutrons

DOSE RANGE (Gy)	FERMILAB Patients	Compl.	%±SE	TAMVEC Patients	Compl.	%±SE
<19.5	-	-	-	5	0	0
20(±0.5)	1	0	0	4	0	
21(±0.5)	9	0		7	2	27±13
22(±0.5)	6	1		4	1	
23(±0.5)	4	0	13±9	-	-	-
24(±0.5)	5	1		4	3	75±22
25(±0.5)	3	1	22±14	-	-	-
26(±0.5)	6	1		-	-	-
>26.5	17	7	41±12	-	-	-
TOTAL	51	11	21.6	24	7	29.2
MEDIAN	28(±1)			23(±1) Gy		
STD. DEV.	5			3 Gy		
5% RISK LEVEL	20		(19.7)	18 Gy		(17.98)

(b) Photons

DOSE RANGE (Gy)	Patients	Compl.	%±SE
65	4	0	0
66-70	29	3	11.5 ±4
71-75	23	3	
76-80	6	2	44±17
80	3	2	
TOTAL	65	10	15.6
MEDIAN	85(±3) Gy		
STD. DEV.	13 Gy		
5% RISK LEVEL	63 Gy		

Table 6.

Normal Tissue Reaction Rates in Relation to TDF Estimates

	TAMVEC		FERMILAB		PHOTONS		TOTAL		
Range	Pts.	Compl.	Pts.	Compl.	Pts.	Compl.	Pts.	Compl.	%±SE
<100	6	0	16	2	4	0	26	2	8±5
100-104	6	0	5	0	9	2	20	2	10±6
105-109	5	2	3	1	16	1	24	4	17±7
110-114	3	1	4	0	14	2	21	3	14±7
115-119	-	-	11	4	14	3	25	7	28±9
120-124	4	4	10	4	3	1	17	9	53±12
125-129	-	-	2	1	5	2	7	3	43±18
TOTAL	24	7	51	12	65	11	140	30	(21)

*Median TDF = 126(±2), standard deviation = 17,
5% risk level is 98

Fig. 1

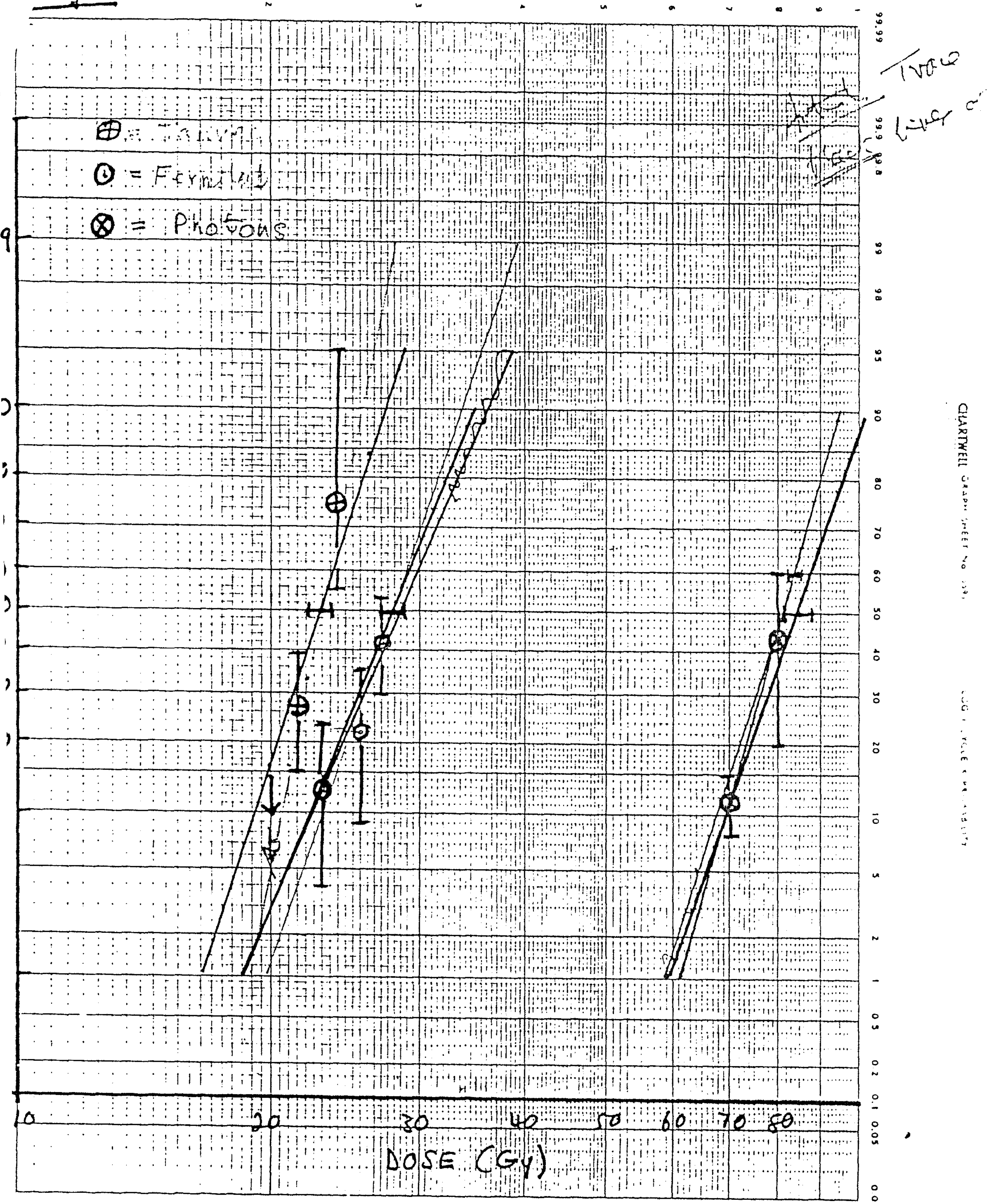
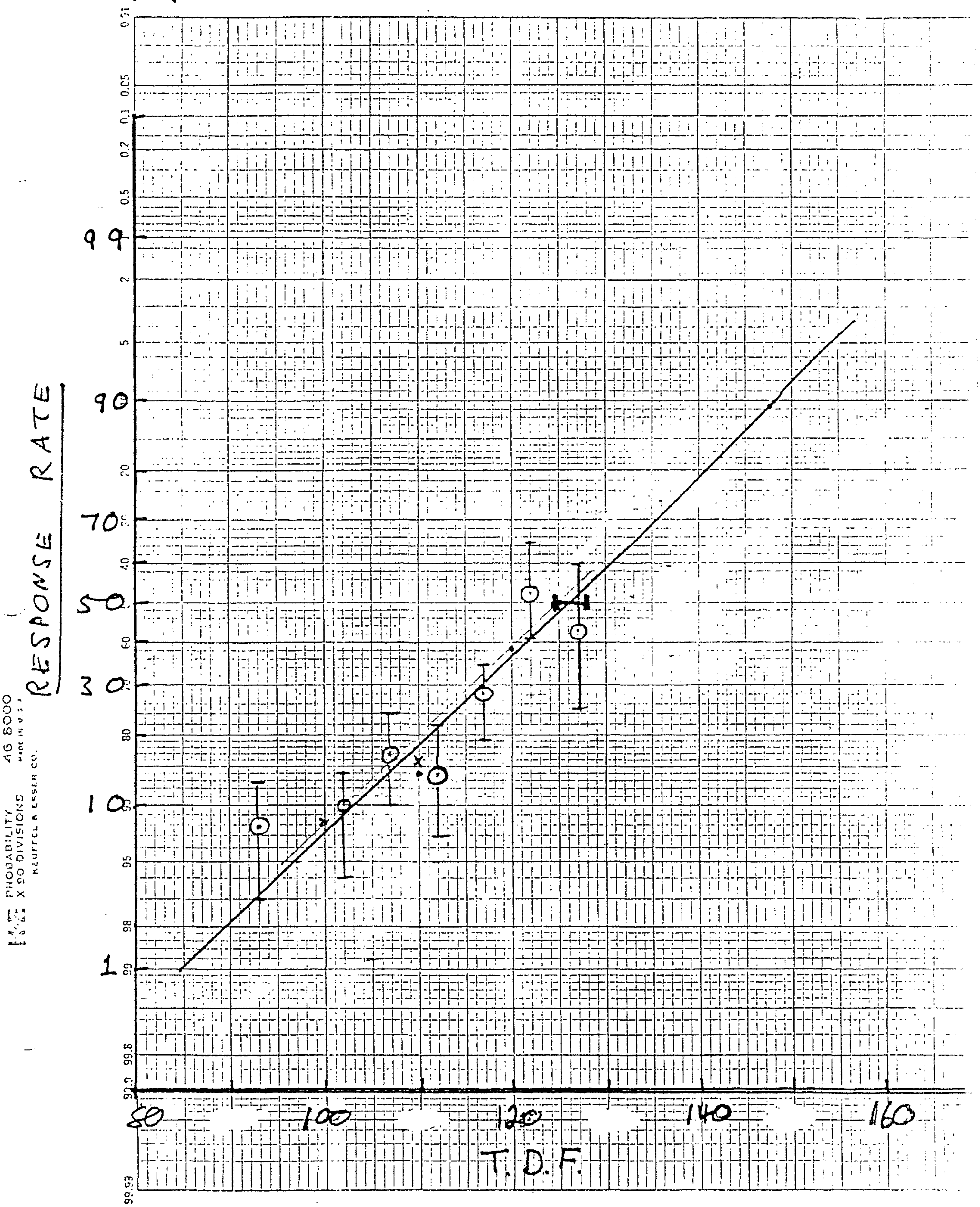


Fig. 2



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Neutron Therapy Department

December 23, 1981

David Hussey, M.D.
Radiation Therapy Department
M. D. Anderson Hospital
and Tumor Institute
6723 Bertner Avenue
Houston, Texas 77030

Dear David,

I enclose the first draft of our joint publication on tolerance. I think we have a fairly firm grasp on the statistics now and find, perhaps surprisingly, that the RBE of your beam is significantly higher than ours, possibly by as much as 20%.

I would appreciate any comment, criticism, changes or additions you might wish to include.

Very Sincerely Yours,

Lionel/mg

Lionel Cohen, M.D.
Co-principal Investigator,
Neutron Therapy Facility

LC:mg

Phone: (312) 840-3865 • From Chicago: 261-1910/ext. 3865 • FTS: 370-3865 • From Suburbs: 231-6040/ext 3865

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22(±0.5)	6	1		4	1	
23(±0.5)	4	0	13±9	-	-	-
24(±0.5)	5	1		4	3	75±22
25(±0.5)	3	1	22±14	-	-	-
26(±0.5)	6	1		-	-	-
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24(±0.5)	5	1		4	3	75±22
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<100	6	0	16	2	4	0	26	2	8±5
100-104	6	0	5	0	9	2	20	2	10±6
105-109	5	2	3	1	16	1	24	4	17±7
110-114	3	1	4	0	14	2	21	3	14±7
115-119	-	-	11	4	14	3	25	7	28±9
120-124	4	4	10	4	3	1	17	9	53±12
125-129	-	-	2	1	5	2	7	3	43±18
TOTAL	24	7	51	12	65	11	140	30	(21)

*Median TDF = 126(±2), standard deviation = 17,
5% risk level is $\overline{9}8$