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LATE REACTIONS AND COMPLICATIONS*
IN PATIENTS TREATED WITH HIGH ENERGY NEUTRONS

p(66MeV)Be(49MeV)

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ABSTRACT

Normal tissue reactions were studied in 71 evaluable cases followed for at least one year after receiving neutron or "mixed beam" irradiation to total equivalent neutron doses of 20 Gy or more. Acute skin and mucosal reactions were classified as mild to moderate in all cases, and all were considered clinically acceptable. The incidence of late reactions, which included severe subcutaneous fibrosis, trismus, and ulceration or necrosis of skin or gastrointestinal mucosa is described.

Eight out of 22 patients followed for a year or more after neutron doses in excess of 20 Gy showed significant late reactions. Late reactions were also observed in six out of twenty patients treated with a neutron boost of 7.5 Gy following 50 Gy of photons for intraoral cancer, and in 5 out of 9 'mixed beam' cases receiving 9 to 11 neutron Gy with 45 to 50 photon Gy concurrently over a seven week treatment period. Nine out of 20 patients treated with curative doses of neutrons following recurrence after radical photon therapy had excessively severe late effects.

In the neutron only group, all patients were treated over a nominal six week period, but the number of fractions ranged from 8 (once weekly) to 28 (four times weekly). A tentative isoeffect line (dose versus fractions) for cutaneous fibrosis could be drawn with an origin at 20 Gy and a slope of 0.04. A TDF analysis of the whole series suggested a median value, assuming an equivalency factor of 3.00 for our beam, of $TDF = 120 (\pm 10)$ for severe stromal fibrosis and associated complications.



INTRODUCTION

Neutron therapy installations throughout the world differ in their particle energy spectra and RBE values as measured in a variety of biological systems. Comparison of results of clinical treatment in various centers, and particularly determination of equivalent doses for cooperative clinical trials, is a problem of some complexity. Measured RBE values depend not only on the neutron energy spectra, but also on the biological system chosen for study and the dosage or fraction-size used. An 'equivalency factor' (RBE of the beam relative to conventionally fractionated photon therapy), has been estimated to be 3.00 for the relatively high energy p(66MeV)-Be(49MeV), Fermilab neutron beam generated by 66 MeV protons on a 49 MeV thick beryllium target. The corresponding equivalency factors for neutron facilities operating at lower energies would be higher, possibly up to a value of 3.80 for the Hammersmith cyclotron. These values are based on comparisons of photon and total neutron beam doses (which include the gamma component). Under these conditions, tumor response and normal tissue tolerances, at least for acute reactions, appear to be comparable in all centers.

On the other hand, the reported incidence of late effects in patients treated on the basis of these equivalency factors is less consistent. The Cancer Therapy Facility at the Fermi National Accelerator Laboratory has accumulated some three years experience in fairly routine neutron therapy of patients. Initially most referrals were patients with advanced and incurable cancer in whom the effects of modest doses of neutrons could be studied without the risk of severe side effects, but with little expectation of long term survival. More recently radical doses of neutrons or

various mixed beam procedures have been delivered with curative intent in potentially curable patients. In general, the proposed equivalency factor of 3.00 was accepted so that a radical treatment corresponding to 60 Gy of photons or higher would receive 20 Gy or more of neutrons or the assumed biological equivalent with mixed beam procedures. Seventy one patients treated at this dose or higher are evaluable in the sense that they have survived a year or more after irradiation. The subject of this paper is a time dose analysis of these cases designed to relate the dosage associated with late effects with the number of fractions and treatment time in the various treatment groups.

MATERIALS AND METHODS

The 71 evaluable patients were grouped according to the neutron schedule used. All had received radical dosage in excess of 20 neutron Gy, or its biological equivalent with mixed beams, and had survived long enough to evaluate late effects, either 12 months after completion of treatment or beyond the onset of an overt and progressive late reaction. Twenty-two patients had received radical neutron therapy alone, 19 of whom were treated in the head and neck region. The remaining patients include two with carcinoma of the pancreas and one with adenocarcinoma of the rectum. Dosage ranged from 20 Gy up to 23 Gy (with one exception receiving 27 Gy). Fraction number ranged from eight to twenty-eight while the overall time was kept constant (except for 1 case) at six weeks (range 40-45 days). A second group of 29 patients received combined photon plus neutron therapy as a planned procedure. Twenty of these were treated with a standard course of photon therapy first to a relatively wide field followed by a neutron boost to the primary site. The remaining 9 received concomitant mixed beam therapy (photon three days and neutrons two days each week). The photon doses ranged from 41 to 54 Gy given in 20 to 39 fractions over a nominal treatment time of five weeks (range 27-58 days). The neutron component ranged from 7.0 to 11 Gy, in

5 to 14 fractions. A further 20 patients had been referred for the possibility of salvage by radical neutron irradiation after completion of radical photon irradiation. The photon dose in these patients ranged between 30 and 70 Gy, fraction number between 15 and 35, total time between 21 and 49 days. The neutron dose was between 18 and 24 Gy delivered in 11-22 fractions over 30-55 days.

Of the 71 cases, 65 were evaluated one year after the completion of treatment and the remaining six, who had died before this follow-up period, were evaluated at the time of death since the late effects in these were already well established. In each patient, the observable late reaction and its intensity was noted. Reactions were defined as 'mild' when no more than minimal discomfort or physical impairment was observed; 'moderate' when the patient experienced some disability or a significant late change was observed by the physician; 'severe' reactions represented marked functional impairment with unequivocal normal tissue injury such as necrosis or fibrosis.

In patients receiving neutrons only, the effect could be correlated with dosage and fraction number (total time being approximately constant) using a scatter diagram and fitting a Strandqvist-type isoeffect line to the data. With the mixed treatment this type of analysis is not possible but time-dose factors (TDF) could be estimated by using the standard TDF formula (Orton and Ellis)⁴ with appropriate gap corrections, for the photon component, and a modified TDF formula, based on the assumed slope of the isoeffect line for neutrons, together with a normalizing factor for the RBE of the high energy Fermilab beam¹. TDF formulae for the two modalities as used in this analysis were as follows:

$$\text{Photon: TDF} = .001 N (d)^{1.538} (t)^{-.169}$$

$$\text{Neutron: TDF} = .024 N (d)^{1.177} (t)^{-.129}$$

where N is the fraction number, d the dose-per-fraction (in rads) and t the average interval between fractions (in days). Derivation of these formulae is described in the Appendix. TDF values were determined for each case in the study and grouped so that appropriate threshold and median levels for significant late reactions could be determined.

RESULTS

a. Neutrons Only (22 Patients)

Raw data relating to these patients are shown in Table 1 together with calculated TDF factors for each case. Fourteen of the 22 patients showed no significant late reaction, while 8 had some fibrosis in the subcutaneous tissues. Of these, 4 showed a severe and disabling degree of fibrosis with limited mobility (including trismus), 2 with ulceration and necrosis of the buccal mucosa, one duodenal ulcer (patient with carcinoma of the pancreas) and one stenosis of the bowel (carcinoma of the rectum). Clearly, patients receiving less than 21 neutron Gy, appropriately fractionated showed no reactions; all significant reactions appeared in patients who received 22 Gy or more. Calculated TDF values emphasize the relatively steep dose response function in that no patient receiving a TDF less than 114 developed a severe reaction whereas four out of twelve patients with TDF values between 114 and 130 exhibited disabling late effects. TDF factors calculated for the neutron treated group are shown in Fig. 2a. The median TDF for severe late effects appeared to be 116 (± 4).

The isoeffect line for significant late effects in the neutron treated patients is shown in Fig. 1. Clearly the data are insufficient to determine the slope of this line with accuracy, but appears to be compatible with an assumed slope of 0.04 (± 0.04) as suggested by Field, et al^{2,3}. Since all the fractionated treatments were delivered over 6 weeks (40 days) the single-fraction intersect of 20 (± 2) Gy corresponds to nominal or equivalent single neutron dose of 13 (± 1.3) Gy.

b. Mixed Beam Data (29 Patients)

Basic data relating to these cases are shown in Table 2. Of the 29 mixed beam patients 18 showed no reactions, 9 had mild or moderate reactions and two developed severely disabling necrotic lesions. No reactions were encountered in patients receiving a TDF of 98 or less, while two out of the 17 cases with TDF values between 118 and 130 had disabling late effects. TDF factors for this group are illustrated in Figure 2b in which the median value for significant late effects appears to be 122 (± 4). It is doubtful whether any significance can be attached to the apparently higher median TDF value for late radiation injury in the mixed beam cases (122), compared to that in those receiving neutrons only (116), but if this difference is real, it suggests that the equivalency factor for neutrons may have been underestimated by 5 (± 3) percent.

c. Neutrons After Late Recurrence (20 Patients)

Data on this series of patients, shown in Table 2c, are relatively scanty because most cases in this category had uncontrolled cancer and did not survive long enough to show established late effects. Sixteen out of the 20 who did survive developed severe or moderate late effects. TDF estimations in this series of cases are complicated by the long gap between the photon and neutron components of the treatment, ranging between six months and twelve years, necessitating the use of large correction factors for recovery during these periods. Estimated TDF factors in this group range between 120 and 240. No median value can be identified.

Pooled TDF values for the whole series is illustrated in Fig. 3. Patients receiving primary treatment (either neutrons alone or mixed beam) appear to form a homogenous group with significant reactions centered around a median TDF of approximately 120 (± 10). The small skewed tail

extending to the right of the distribution (TDF >140) consists entirely retreated, recurrent cases.

DISCUSSION

The data presented in this report are clearly too scanty to define dosage and time parameters, as they affect normal tissue tolerance, with any great accuracy. However, since a small but real incidence of high-dose effects was observed, the doses used clearly approximate the limits of normal tissue tolerance and must be close to the optimal levels for the various systems studies. Doses below 20 Gy appear to be well tolerated by all normal tissues traversed by the neutron beam (in the neutron only group), with the possible exception of the central nervous system which was carefully excluded from the target volume in this series. Specifically, the skin and subcutaneous tissues, the buccal mucosa and oropharynx, the temporomandibular joint, peripheral and cranial nerves, gastrointestinal mucosa, and connective tissues in general, have not shown severe or long lasting late changes in this dosage range. On the other hand, doses of 21 Gy and over have produced some severe side effects such as massive subcutaneous fibrosis, disabling trismus, necrotic ulceration of the mucosa of the oropharynx and perforating ulcers in the duodenum. This narrow range suggests a very steep dose-effect curve for this modality.

We were unable to demonstrate significant recovery with increasing fractionation in any of the systems studied. Severe reactions were observed in the same dosage range between 11 and 25 fractions. The data is clearly compatible with an isoeffect line of zero slope with a median nominal single neutron dose for late radiation injury of 14.7 Gy, but is equally well fitted by a line of slope 0.08 with a median nominal single dose of 12.0 Gy (incremented by an over-all time correction factor of 1.50 for 6 weeks' treatment). These results appear to be compatible with the suggestion by Field et.al.² that an appropriate isoeffect slope for neutrons would be 0.04 (± 0.04).

A TDF analysis is valuable in a study of this nature if the mixed beam results are to be included. TDF values of the order of 115 (± 10) describe the median range for significant reactions in both the neutron and mixed beam cases. (Retreated patients are clearly a distinct subset and should be excluded from the analysis). Separating the neutrons only and mixed beam groups show the median TDF values to be marginally higher in the latter, possibly indicating a small error in the biological equivalence factor used. One could conclude a TDF value as high as 116 may be well tolerated in the mixed beam situation (at least with the neutron to photon mix used in these treatments).

REFERENCES

* This work was supported by NCI Grant 5 PO1 CA18081.

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3. Field, S. B. , "An Historical Survey of Radiobiology and Radiotherapy with Fast Neutrons". Current Topics in Radiation Research II; 1-86 1976.
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TABLE 1

Patients Treated with Neutrons Only

#	Area	Dose (D)	Fractions (N)	Time (T)	TDF *	Reaction
77-075	Trachea	2000	20	40	99	---
77-002	Salivary	2000	11	40	102	---
78-076	Orbit	2000	8	40	103	---
77-045	Hypopharynx	2100	14	40	107	---
77-098	Parotid	2100	14	40	107	---
77-094	Antrum	2100	14	40	107	---
77-124	Nasopharynx	2100	14	40	107	Mild
76-019	Oral cavity	2200	22	22	108	---
76-079	Oropharynx	2200	22	40	110	---
78-004	Parotid	2200	23	40	110	---
77-118	Oropharynx	2240	28	40	111	Mild
78-073	Pancreas	2210	13	45	112	---
77-052	Parotid	2200	15	40	113	Mild
77-071	Mouth	2200	11	40	114	Severe
78-094	Parotid	2200	11	41	114	---
77-129	Pancreas	2300	25	40	115	Severe
77-020	Lacrimal	2300	23	40	116	---
76-022	Hypopharynx	2300	23	40	116	---
78-148	Tongue	2350	19	45	118	Moderate
77-008	Palate	2325	14	40	120	Severe
77-127	Rectum	2700	18	99	126	Severe
78-057	Parotid	2400	12	31	130	---

*Neutron TDF = .024 x N (D/N)^{1.177} (T/N)^{-.129}

TABLE II
MIXED AND SEQUENTIAL PHOTONS + NEUTRONS

#	Area	Photons		Neutrons		Total	TDF*	Reaction
		Dose	Frac	Dose	Frac	Time		
76-003	Antrum	4140	25	700	7	52	95	----
76-078	Nasopharynx	5000	39	700	7	70	99	----
76-005	Tonsil	4500	28	700	7	55	99	Mild
78-095	Supraglottic	4200	28	980	14	93	99	Moderate
76-024	Parotid	4400	22	700	7	49	106	----
78-059	Hypopharynx	4600	23	910	14	108	107	----
78-110	Oropharynx	4200	21	1022	14	86	109	----
77-059	Tongue	5000	28	700	7	64	110	----
78-082	Oropharynx	4200	21	1120	14	110	110	Moderate
78-010	Tongue	4860	27	750	5	56	112	----
77-039	Larynx	5000	29	750	5	55	113	----
76-008	Tonsil	4620	21	700	7	44	114	----
77-080	Hypopharynx	5000	29	750	5	53	114	----
78-027	Tongue	5040	28	750	5	48	118	Severe
77-113	Tonsil	5000	25	750	5	49	120	----
78-052	Tongue	5075	29	750	5	43	120	Moderate
77-043	Parotid	5000	25	750	5	47	121	Mild
77-105	Parotid	4674	22	900	6	52	123	----
78-067	Parotid	5000	25	800	5	52	123	----
78-047	Nasal Cavity	5000	25	750	5	44	123	----
78-124	Salivary	5000	25	800	4	49	123	----
77-021	Oropharynx	4500	20	910	13	45	123	----
78-127	Inguinal Area	5000	25	800	5	52	123	Mild
78-072	Tongue	4500	20	910	13	45	123	Mild
78-025	Larynx	4500	20	910	13	45	123	Mild
78-032	Larynx	4420	23	1050	7	51	125	Severe
77-076	Tongue	5408	27	750	5	47	130	----
78-099	Tongue	5000	25	890	5	48	130	Moderate
77-017	Tongue	5000	25	1000	10	55	131	----

$$*TDF = .001 \times N \left(\frac{D_P}{N_P} \right)^{1.538} \left(\frac{T}{N} \right)^{-.169} + TDF_n \text{ from Table I}$$

TABLE III
NEUTRONS AFTER LATE RECURRENCE

#	Area	Photons			Gap Months	Neutrons			TDF *	Reaction
		Dose	Frac	Time		Dose	Frac	Time		
77-056	Antrum	3000	15	21	28	1800	18	43	120	Severe
76-023	Hypopharynx	3000	15	21	85	2200	22	56	134	Severe
76-013	Epiglottis	2000	5	5	10	5000 ³ / ₇₀₀	20/7	55	144	Moderate
77-100	Parotid	5050	25	35	28	2000	20	50	154	----
76-013	Neck Nodes	2000	5	5	10	2400	14	46	155	Moderate
78-170	Neck Nodes	7000	35	45	1	960	6	16	160	Severe
78-079	Salivary	6000	30	42	144	2100	14	58	160	Severe
77-107	Tongue	5500	35	49	6	2000	20	50	163	Severe
78-090	Larynx	4800	24	34	24	2100	14	(40)	163	Severe
77-096	Antrum	6090	30	42	10	1800	12	36	170	----
78-044	Lacrimal gland	5000	25	30	48	2200	10	36	171	----
77-110	Orbit	7000	35	45	120	4000 ³ / ₉₀₀	20/6	50	171	----
78-071	Shoulder	5000	25	35	192	2400	15	(40)	171	Severe
78-053	Tongue	6612	35	45	60	750/ 5075	30	56	172	Moderate
77-022	Nasopharynx	7000	35	49	36	2100	21	46	184	Severe
77-079	Neck	6600	35	49	22	2200	11	37	193	Severe
77-014	Buccal mucosa	7000	35	64	12	5000 ³ / ₇₀₀	25/7	56	194	Moderate
77-019	Buccal mucosa	6600	33	49	22	2200	11	37	195	Moderate
78-122	Salivary	9000	45	151	36	2004	12	48	204	Moderate
78-170	Max. Sinus	9700	40	60	84	2500	16	51	242	Moderate

* as defined on Tables I & II

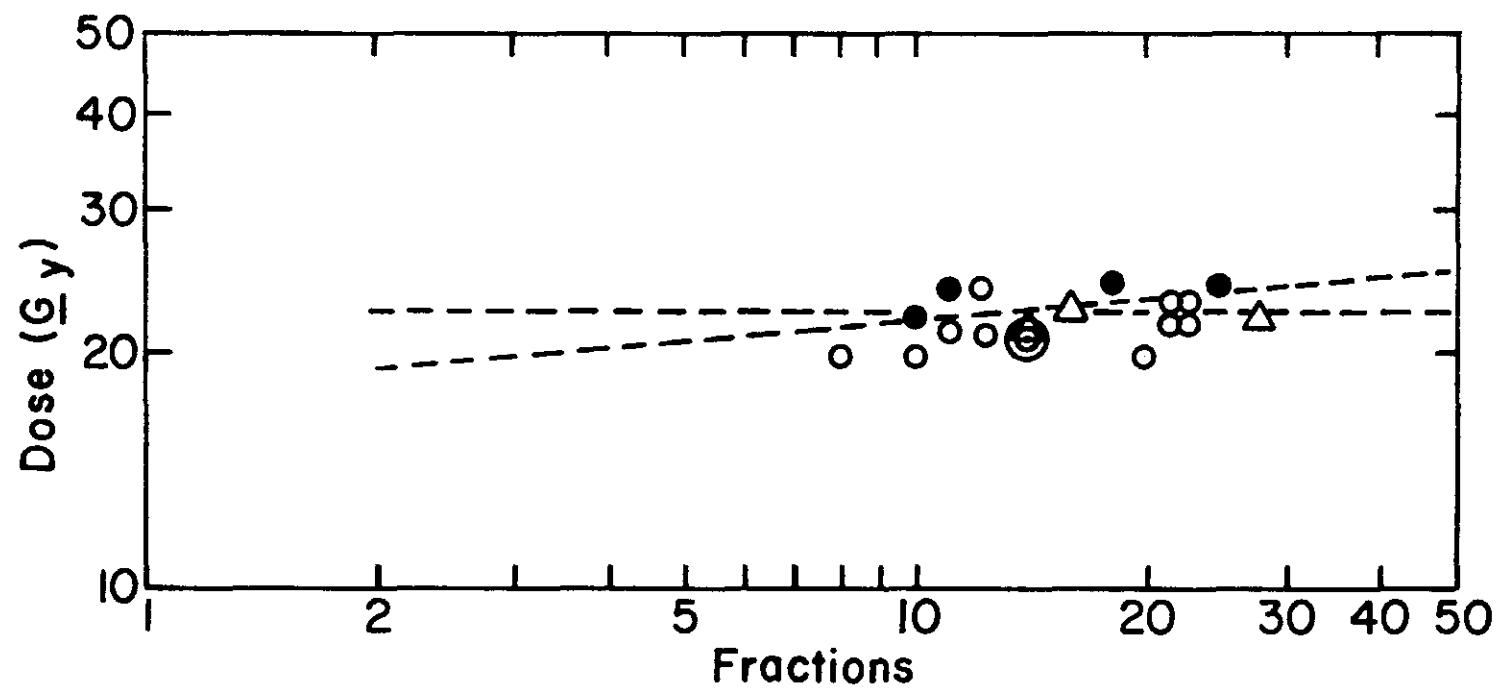


Fig. 1. Isoeffect line for 22 patients treated with neutrons over 6 weeks with varying doses, and fraction numbers ranging from 8 to 25. 0 = No significant reaction; Δ = mild reaction; \bullet = severe or disabling late effects.

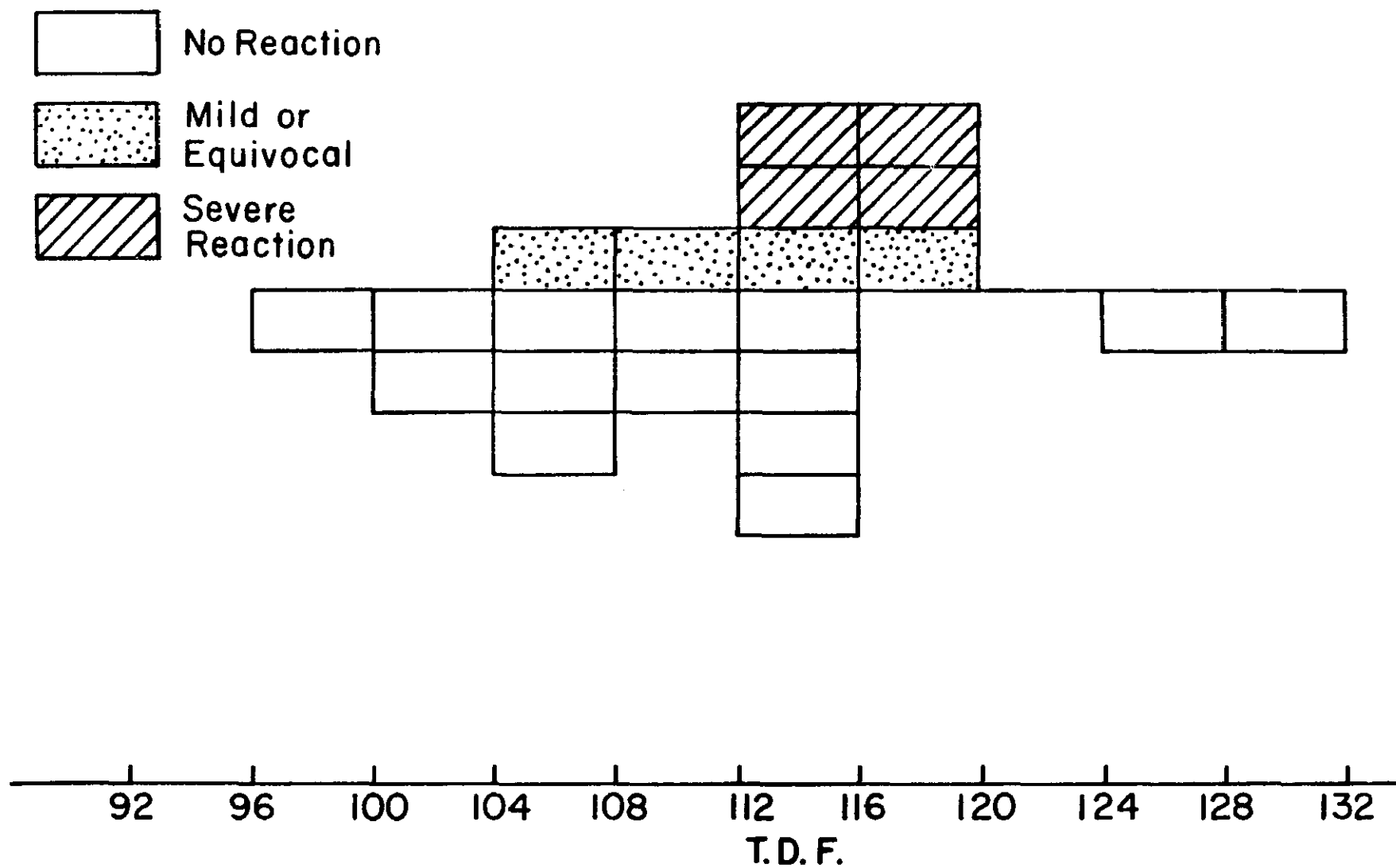


Fig. 2a. TDF factors and corresponding reactions in 22 patients treated with neutrons only.

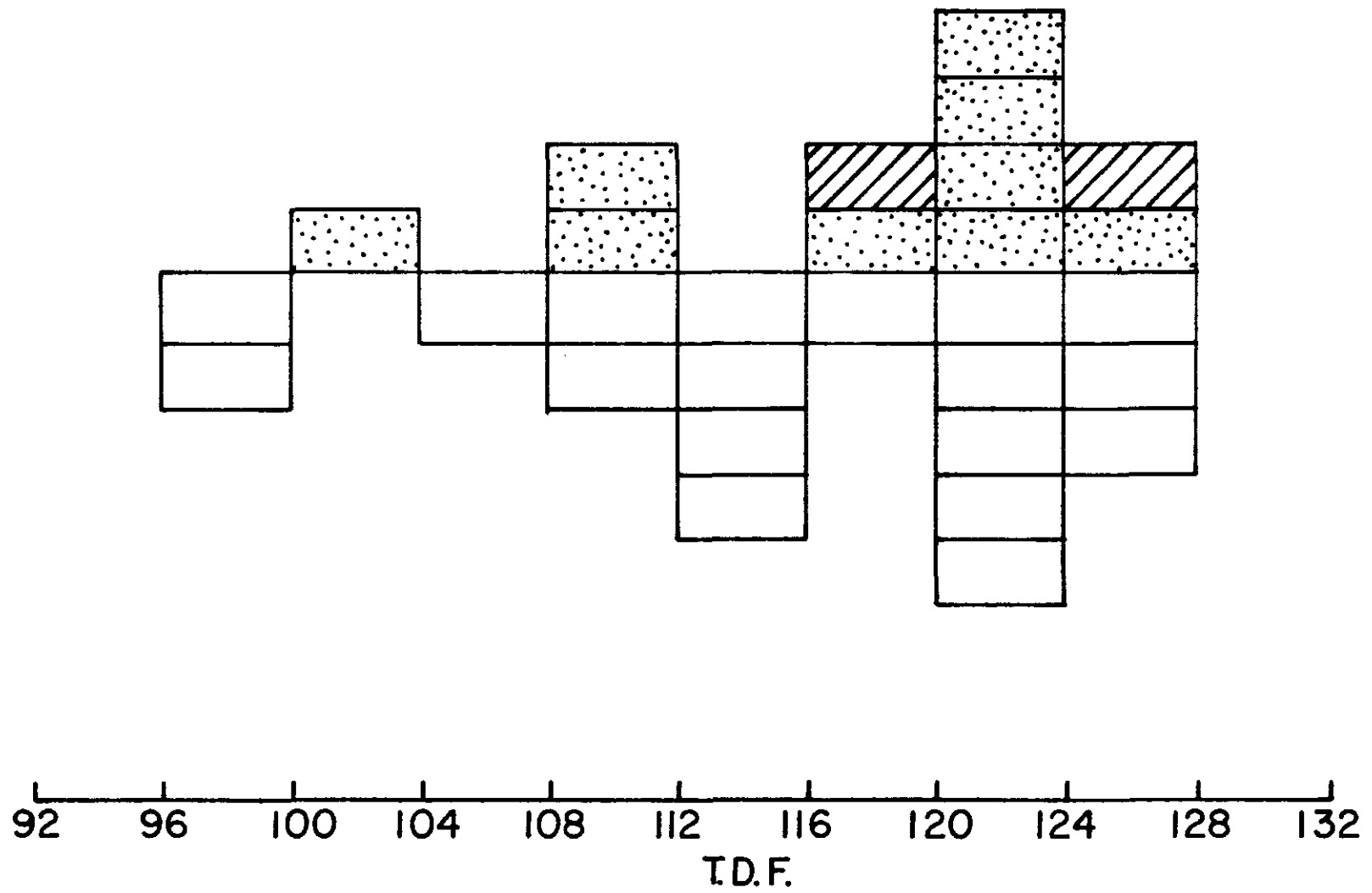


Fig. 2b. TDF factors and corresponding reactions in 29 mixed beam cases.

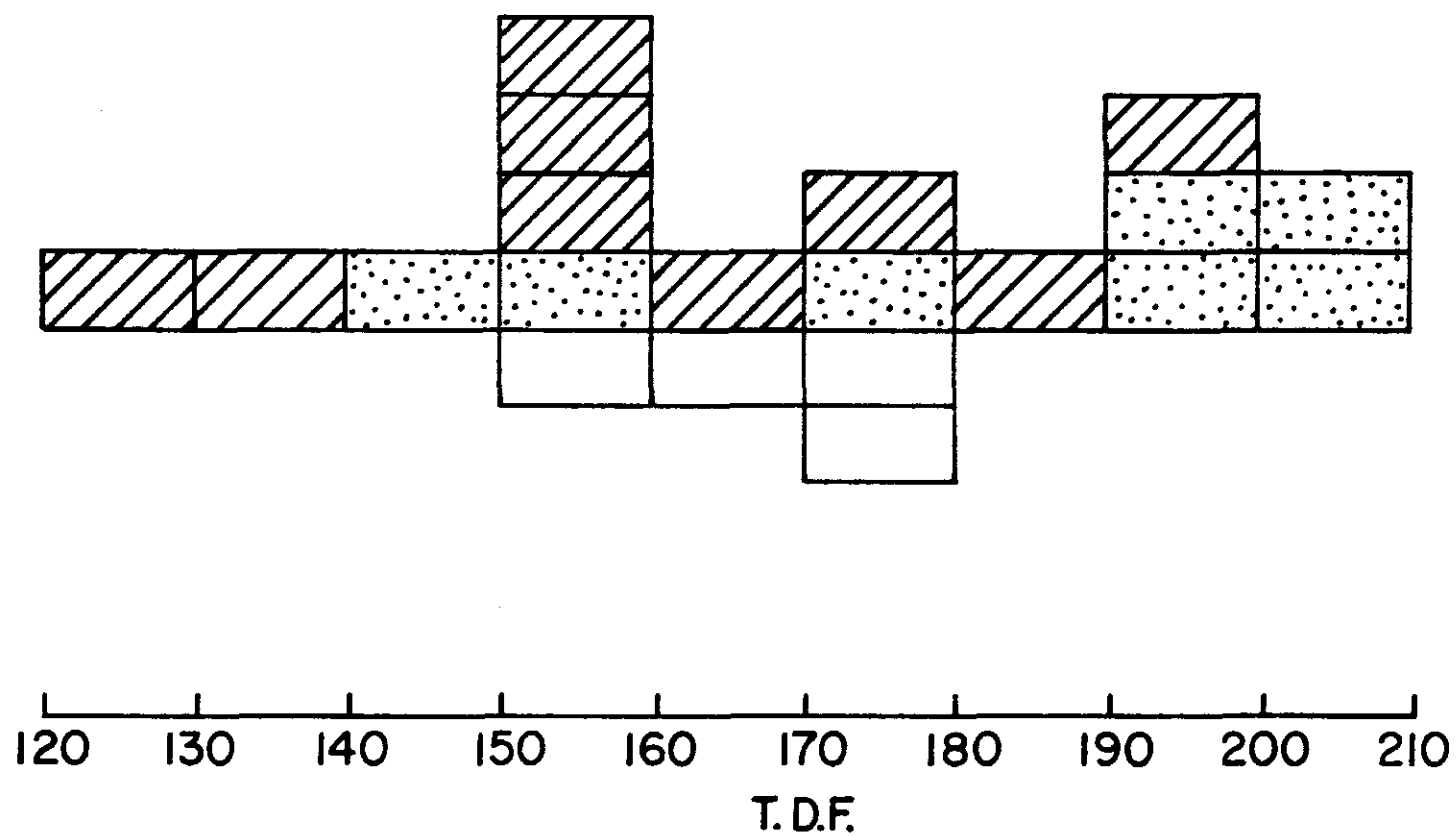


Fig. 2c. TDF factors and corresponding reactions in neutron given for late recurrence after a full course of low LET therapy.

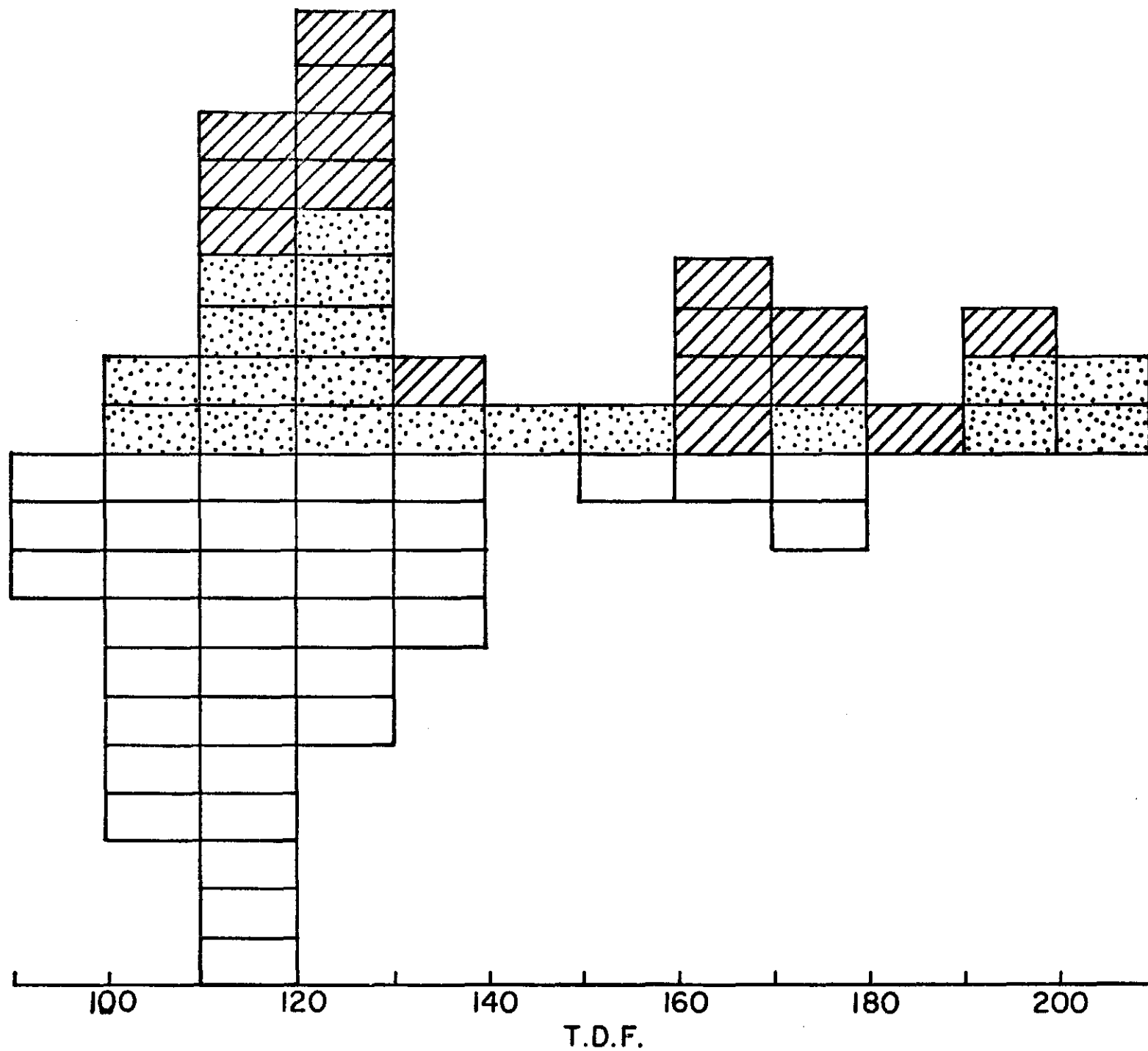


Fig. 3. Pooled results of all cases in relation to calculated TDF values.

APPENDIX: Derivation of TDF for mixed-beam
(photon + neutron) irradiation.

The nominal single dose (NSD) for treatment with a dose of D rads delivered in N fractions over T days is given by the conventional Ellis formula,

$$NSD = D \times N^{-\alpha} \times T^{-\beta}$$

where the exponents $\alpha = 0.24$ for low LET radiations, $\alpha = 0.04$ for neutrons⁽³⁾, and $\beta = 0.11$ independent of modality or beam quality. The TDF formula is derived from the NSD equation such that,

$$TDF = K \times (NSD)^{1/(1-\alpha-\beta)}$$

where K is a normalization constant ($K = .001$ for photons). Conventionally, TDFs are calculated for a given fraction size $d = D/N$ and a specified interval between fractions $t = T/N$, and,

$$TDF = K \times N \times d^{\delta} \times t^{-\tau}$$

where $\delta = 1/(1-\alpha-\beta)$ and $\tau = \beta\delta$. Since the exponent of N is unity, this formula allows for additivity of TDF values in concomitant or sequential courses.

Numerically, for photons $\delta_{\gamma} = 1.5385$ and $\tau_{\gamma} = 0.1692$; for neutrons $\delta_{\nu} = 1.1765$ and $\tau_{\nu} = 0.1294$. The normalization constant for neutrons (K_{ν}) is derived from clinical observation. For example, if 6000 rads of photons given in 30 fractions over 40 days are considered equivalent to 1950 rads of neutrons given in 13 fractions over 39 days, then

$$TDF_{\gamma} = .001 \times 30 \times 200^{1.5385} \times 1.33^{-0.1692} = 99.1 \text{ and,}$$

$$TDF_{\nu} = K_{\nu} \times 13 \times 150^{1.1765} \times 3.0^{-0.1294}$$

The two TDF estimates are equal when $K_{\nu} = .024$.

In a mixed beam procedure where the two modalities are used concomitantly or alternately, the composite $TDF_{\sigma} = TDF_{\gamma} + TDF_{\nu}$. If a course of low LET therapy is followed, after a gap of some days by a neutron boost,

$$TDF_{\sigma} = TDF_{\gamma} \times \left(\frac{T_{\gamma}}{T_{\gamma} + \text{GAP}} \right)^{0.11} + TDF_{\nu}$$

where T_{γ} is the total treatment time for the first (low LET) course and GAP is the interval in days between the two courses.

Note that rads have been used instead of Grays in this Appendix in order to remain compatible with conventional notation and normalization processes in TDF calculations.