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Absence of a Demonstrable Gain Factor  
for Neutron Beam Therapy of Epidermoid Carcinoma  
of The Head and Neck.

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Abstract

A comparison of normal tissue and tumor responses in patients treated with the high energy Fermilab neutron beam and conventional photons (Cobalt and 4 MeV x-rays), yielded the following parameters. For neutrons the median dose for significant radiation injury in the irradiated tissues was 31 (+2) Gy and the median dose for local control of the tumor was 26 (+2) Gy. The corresponding doses for photons were 90 (+4) Gy for normal tissue injury and 74 (+3) Gy for local control of the tumor.

These figures show that the therapeutic ratio is roughly 1.2 for both neutrons and photons.

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 local control rate was the same for both modalities (44%).

Key words: epidermoid carcinoma, neutrons, dose effect relationship, gain factor.

INTRODUCTION

The effect of neutron beam therapy on the response of late stage cancer of the head and neck is at the present time the most widely studied clinical system. Reports from Amsterdam<sup>1</sup>, London (Hammersmith)<sup>2</sup>, Houston (TAMVEC)<sup>3</sup>, Edinburgh and Essen (EORTC, this conference) and Chicago (Fermilab, unpublished data) now total some 270 patients treated with neutrons alone (excluding mixed beam studies) and 272 patients treated with photons either in concomitant pilot studies or in randomized clinical trials. In general the local control rate has been consistently greater with neutrons, although the statistical validity of this observation remains to be tested. There is also a marked variation in results among the different centers. A particularly striking difference was observed in the Hammersmith series<sup>2</sup> in which a highly significant difference in local control has been reported. Other centers have shown a marginal improvement with neutrons, but the differences so far are not statistically significant. Furthermore, in all reported series the complication rate has been higher with neutrons, suggesting that the advantages observed with the new modality might be attributed to a relatively higher dosage level. This could occur because of uncertainties in the RBE for late tissue damage and also to differences in dosimetry and treatment plans among centers.

In particular, published reports on therapy technique and treatment plans from Hammersmith<sup>2</sup> show that prescribed doses in that institution are in fact minimum tumor doses (in contrast to the protocols in the United States which prescribed target absorbed doses) and that a high degree of uniformity in dosage distribution is obtained throughout the target volume (without significant hot spots). The target volume is small and generally confined to the primary tumor and any palpable nodes, but does not include elective irradiation of sites of potential regional metastases. These constraints might be expected to be associated with better local control and fewer local complications, but may well be offset by a greater risk of marginal and regional recurrence. It is significant that differences in overall survival of patients treated with the two modalities are considerably less striking than in the case of local control rates.

Because of the discrepancies in the results obtained in the various centers, it seemed appropriate to study the dose effect relationships for neutrons and photons, evaluating tumor response and normal tissue injury with both modalities. During the past five year experience at Fermilab, sufficient data have accumulated for a tentative study of this nature.

METHODS AND MATERIALS

The Fermilab Neutron Therapy Facility has a fixed horizontal beam of neutrons generated by the  $p(66)Be$  reaction, which is appropriately collimated and delivered in an isocentric mode to patients immobilized in a sitting position in a rotating chair. Skin sparing, depth dose, dosage distributions and treatment plans are essentially similar to those obtainable with 4 MeV photons. Patients were generally treated with target absorbed doses between 22 and 27 Gy to the primary target volume which was designed to encompass the primary tumor with a 2 cm margin. The uninvolved neck was treated electively with about two-thirds of this dosage. Treatment was delivered over a fairly consistent overall time of around six weeks at two or three fractions per week (13 to 19 fractions). A tentative RBE of about 3 was assumed.

Although this was not a randomized study, eligibility criteria and treatment techniques generally followed the current national protocol (RTOG 76-10), except that total target absorbed doses varied more widely than the limits prescribed by protocol. For comparison an essentially similar group of patients from the same referring centers who had been treated by photons (as the control arm in a

randomized study) were similarly analyzed. Since this is not a controlled randomized study, the two arms may not be strictly comparable. The majority of patients receiving neutrons alone (as distinct from mixed beam) elected to have neutron therapy for personal or logistic reasons, though all patients in both arms had T3 to T4 lesions with or without cervical nodes. It is possible, of course, that the neutron group included some patients with more advanced disease who were referred for this modality without randomization because of physician preference, in the belief that prognosis with conventional therapy might be poor.

During the period under review, 43 evaluable patients had been treated with neutrons and 73 with conventional low LET techniques (photons and electrons). Results were evaluated at a minimum of two years after completion of treatment. The results were expressed in terms of persistent tumor control within the target volume and the appearance of significant late effects attributable to the radiation. It is necessary to emphasize that this is a first tentative evaluation. Differences in size, stage, site of origin and patient performance status have not been taken into account. The neutron group may well represent more advanced disease and include a number of post-surgical recurrences. Furthermore, all doses analyzed are the given target absorbed doses. Since tumor control depends largely on minimum target

volume dose and complications are likely to correlate best with maximum tissue doses, a more detailed dosimetric analysis may lead to different conclusions. A comprehensive report on this series of patients, together with data on a variety of mixed beam and "boost" procedures, all analyzed in terms of local control, survival and complications for tumors of various stages and specified sites of origin, is in the course of preparation

## RESULTS

Of the 73 patients treated with photons, 32 remain free of tumor within the target volume yielding a local control rate of 44% ( $\pm 6\%$ ). Of 43 patients treated with neutrons there were 18 local controls, a control rate of 43% ( $\pm 7\%$ ). There were also 4 significant complications in the photon series, and 8 in the neutron group.

Results of the dose effect analysis for the neutron treated patients are shown in Table 1 and the corresponding analysis for the photon controls in Table 2. Probit analysis of the four dose effect functions (tumor and normal tissue, photons and neutrons) 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. With photons the median dose for normal tissue injury was 90 ( $\pm 4$ ) Gy and for local control of the tumor 74 ( $\pm 3$ ) Gy. Figure 1 shows the data points with their associated standard deviations and the dose effect functions based on the derived parameters in the probit equation. Dosage is expressed in terms of the target absorbed dose.

Figure 2 shows the computed conditional probability of uncomplicated control as a function of target absorbed dose. The probability of uncomplicated control is given by the formula:

$$PUC = P_t (1 - P_n)$$

where  $P_t$  represents the probability of local control and  $P_n$  the probability of significant normal tissue damage at the dose in question. It will be noted from Figure 2 (line b) that a well defined optimal target absorbed dose exists (approximately 27 Gy) where the probability of uncomplicated control with neutrons is maximal. At this dose the estimated probability of uncomplicated control is about 45%. Similarly with photons the optimal target absorbed dose is around 78 Gy with a similar probability of uncomplicated cure.

DISCUSSION

The median doses for the four contingencies computed by probit analysis (or the position of the four lines in Figure 1) show that the therapeutic ratio (ratio of the median dose for normal tissue injury to the median dose for tumor control) is 1.20 ( $\pm 0.17$ ) for neutrons and 1.21 ( $\pm 0.16$ ) for photons which are not significantly different. Similarly, the RBE of neutrons relative to photons for normal tissue tolerance was 2.9 ( $\pm 0.2$ ) and for tumor control 2.9 ( $\pm 0.3$ ), which are virtually identical. The therapeutic gain factor of neutrons relative to photons (ratio of RBEs) under these conditions does not differ significantly from unity.

From this analysis it must be concluded that neutrons are unlikely to offer a significant advantage (in terms of cure rate) in the management of late stage epidermoid carcinomas of the head and neck. The optimal dose with either modality could yield a local control rate of about 60%, with a 25% risk of significant radiation injury, and an estimated probability of uncomplicated control of no more than 45%. It is unlikely that any adjustment of dosage would improve these results substantially.

An interesting consequence of this analysis is the potential for improving results by more detailed attention to treatment planning so as to achieve uniformity of dosage distribution throughout the target volume. Lines a and c in Figure 2 represent the comparison between tumor response and normal tissue injury when the former is evaluated in terms of minimum tumor dose (that is assuming absolute uniformity throughout the target volume). Under these conditions the optimal dose is lower and the probability of uncomplicated control substantially higher than that obtained with the less uniform distribution. This result is a direct consequence of the very steep dose response functions observed. Whether a significantly better outcome would result from improved uniformity of dosage in the target volume, and whether this would be better achieved with neutrons than with photons or other low LET radiations (electrons or protons), remains to be determined.

These conclusions apply to epidermoid carcinoma of the upper respiratory and alimentary tract. They may also be true for epidermoid cancers in other situations such as the uterine cervix.

Non-epidermoid carcinomas have been excluded from this analysis although several such cases, including adenocarcinomas, adenocystic tumors and cylindromas were

treated. It is noteworthy that most of these were well controlled by neutrons in the same dosage range (Kurup et al., unpublished data) and would have demonstrated a significant superiority of neutrons had they been included in the series. The implications are that while the advantages of neutrons for epidermoid cancer are marginal at best, neutrons may afford a real advantage in the treatment of adenocarcinomas and other radioresistant tumors.

References

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Table 1Neutrons

<u>Dose (Gy)</u>	<u>Patients</u>	<u>Controls</u>	<u>Compl. %</u>	<u>Rates</u>	
				<u>Cure %</u>	<u>Compl. %</u>
≤ 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	43(+7)	19(+6)

Medians Control 26(+2)Gy; Complications 31(+2)Gy.

Table 2Photons

<u>Dose (Gy)</u>	<u>Patients</u>	<u>Controls</u>	<u>Compl. %</u>	<u>Rates</u>	
				<u>Cure %</u>	<u>Compl. %</u>
<u>&lt;62</u>	5	0	0	0	0
63 - 67	3	0	0		
68 - 72	42	19	1	45 ( <u>+8</u> )	2 ( <u>+2</u> )
73 - 77	15	8	2		
<u>≥78</u>	8	5	1	57 ( <u>+10</u> )	13 ( <u>+7</u> )
TOTAL	73	32	4	44 ( <u>+6</u> )	5 ( <u>+3</u> )

Medians Control 74 (+3)Gy; Complications 90 (+4)Gy

LEGEND

Figure 1: Four dose effect functions for tumor control and complications with neutrons and photons. The error bars shown are standard errors for the grouped data from Tables 1 and 2. The curves represent the function fitted to the data using the probit method. Because of the small numbers involved there is some uncertainty in regard to the complication rate for photons (shown as a broken line).

Figure 2: Calculated probabilities of uncomplicated control and optimal doses for neutrons and photons derived from the four functions shown in Figure 1 (lines b and d). These two functions relate to target absorbed doses as indicated in the Tables. Both modalities yield a maximum probability of uncomplicated control of the order of 40%. Lines a and c represent an idealized situation relating to a prescribed minimum tumor dose, assuming absolute uniformity throughout the target volume. In this instance there would be a wider separation between the dose effect functions in Figure 1 leading to a higher probability of uncomplicated control, slightly in excess of 50%, for both modalities.

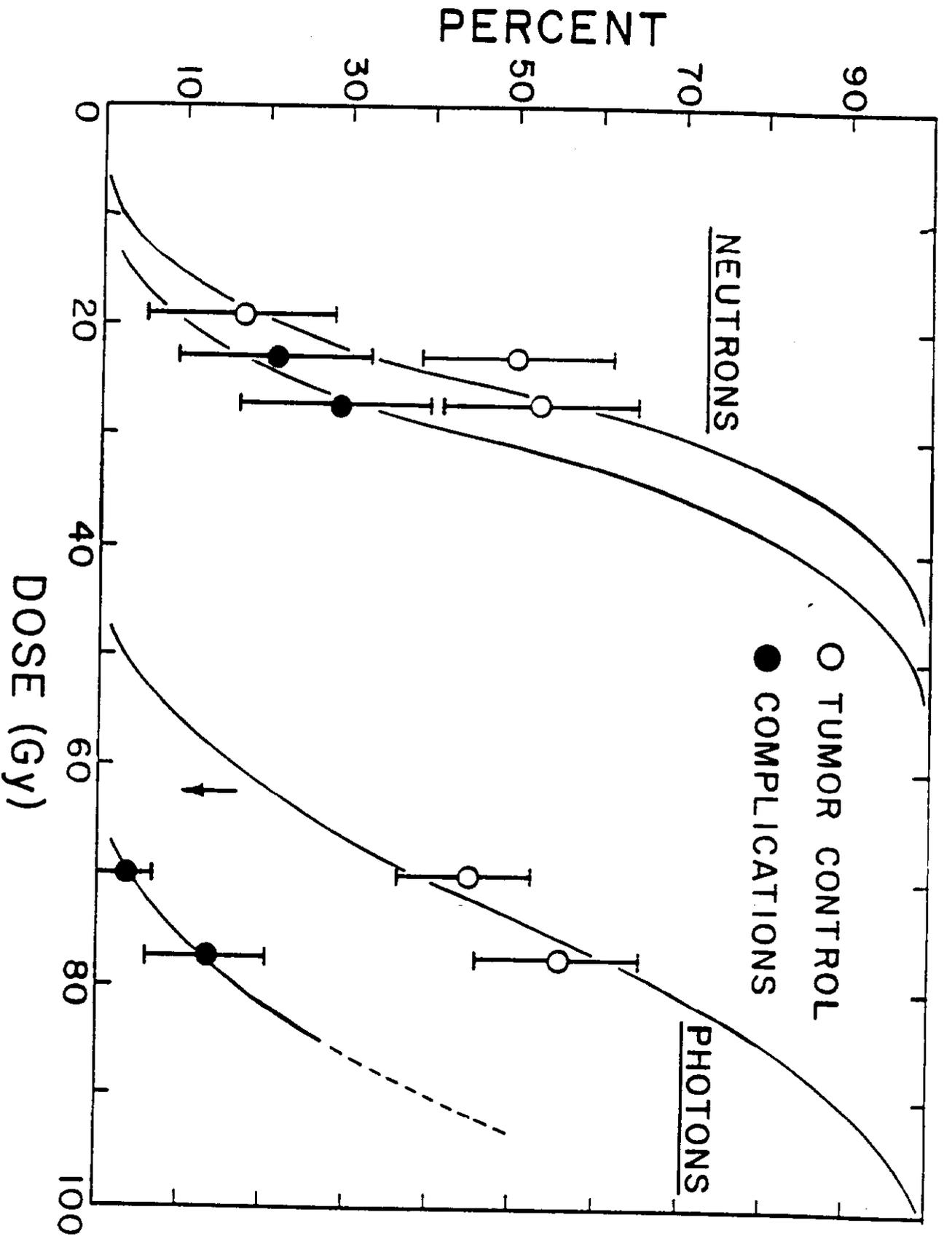


Figure 1

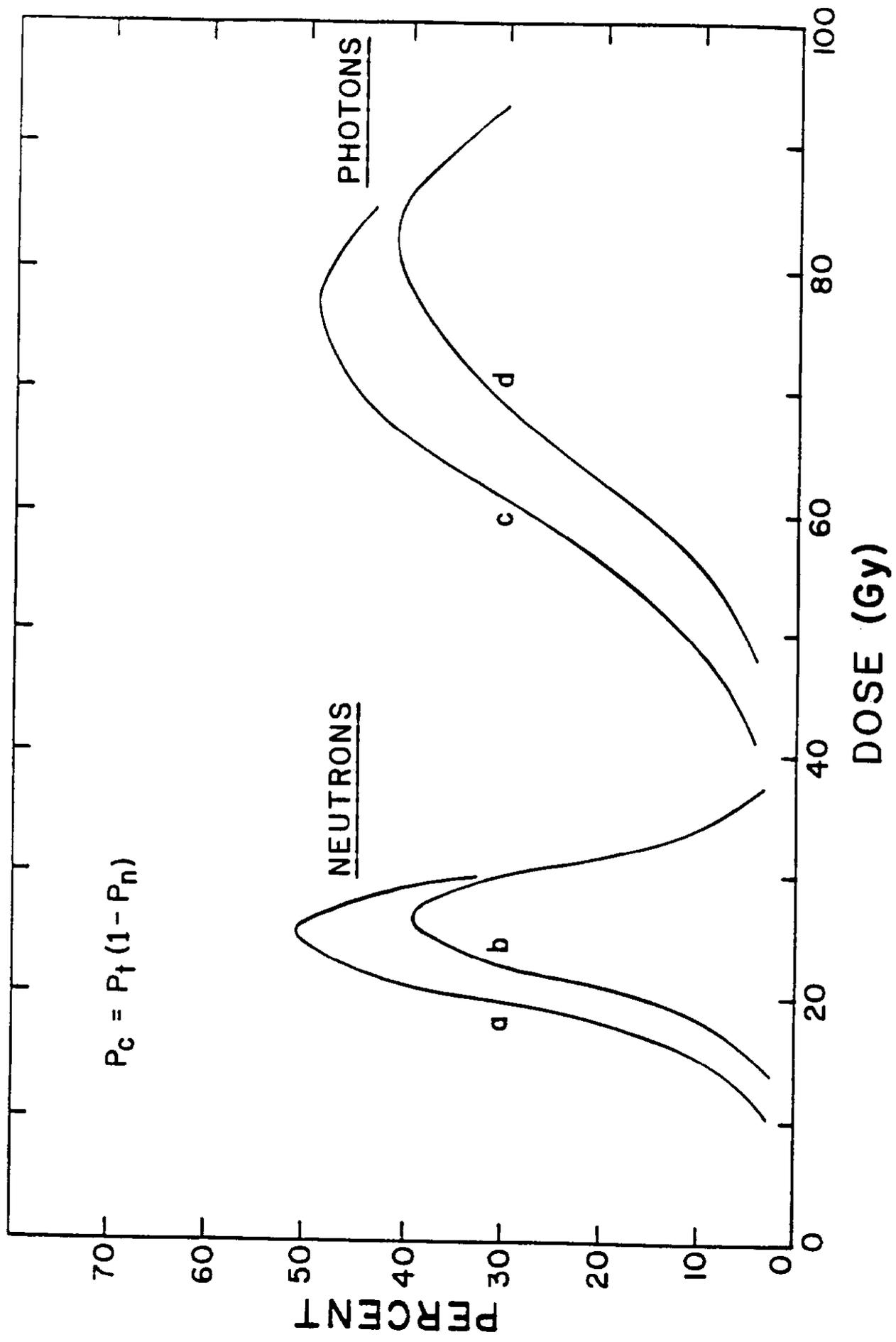


Figure 2