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TOLERANCE OF THE HUMAN SPINAL CORD TO HIGH ENERGY p(66)Be(49) NEUTRONS

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Tolerance of the Human Spinal Cord to High Energy p(66)Be(49) Neutrons

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ABSTRACT

The risk of post irradiation myelopathy was evaluated in 76 patients followed for 1-5 years after neutron irradiation of the cervical and thoracic regions. No overt myelopathy was observed. Forty-six patients had received doses (central cord dose) in excess of 10 Gy, 9 received doses in excess of 12 Gy, and 5 received doses between 13 and 17 Gy, all without any evidence of spinal cord injury. On careful questioning, a subjective transient neuropathy (a tingling sensation in one extremity) was reported by 6 patients, but this was apparently unrelated to dose. A review of available literature revealed a total of 14 patients with myelopathy, 13 of whom received doses in excess of 13 Gy delivered with relatively low energy neutrons generated by the deuteron + beryllium reaction. It is concluded from these studies that the tolerance limit for the human spinal cord irradiated with high energy [p(66)Be(49)] neutrons is close to 15 Gy, above which the risk of cord injury becomes significant. Central cord doses of 13 Gy or less appear to be well tolerated with little, if any, risk of myelopathy. These conclusions are valid for a treatment time of 4 weeks or more with two or more fractions per week (9 or more fractions). The RBE for the human spinal cord irradiated under the above conditions compared with conventionally fractionated photon therapy does not exceed 4.0.

INTRODUCTION

Reactions in normal tissues following therapeutic doses of high energy neutrons are essentially similar to those observed in conventional radiation therapy when the two modalities are given in equivalent doses. In this regard equivalence implies that the relative biological effectiveness (RBE) of the neutron beam compared with megavoltage photons is known precisely. RBE values have been shown to depend upon the energy spectrum of the neutron beam, the fractionation scheme, the tissues irradiated and the endpoint studied. For a given total dose, the response to neutrons is practically independent of fraction size.[7] The observed dependence of RBE upon fraction number is a consequence of the response to the low-LET standard radiation which does depend upon fraction size. Since our knowledge of normal tissue tolerance is largely based upon clinical experience with high doses delivered in multiple small fractions over 5-7 weeks, the equivalency factor, conventionally used in neutron beam therapy, is based upon the RBE for neutrons relative to that for conventionally fractionated photon therapy.

An approximate estimate of the equivalency factor is generally provided by pre-clinical radiobiological studies, determining the RBE in tissue cultures or animal systems, using small fractionated doses. However, since the RBE is tissue dependent, and may even be species dependent, this is a very rough

approximation. The final determination of the clinical RBE requires analysis of reactions in patients who have been treated with appropriate doses and followed for a sufficient period of time to observe the outcome.

It has been established from both animal experiments and clinical observations that the RBE for late reactions, such as fibrosis and ischemic necrosis, is significantly higher than that for acute reactions like epidermolysis and mucositis.[19] This implies that cell populations in late-reacting tissues are more susceptible to depletion by a given dose of neutrons than are the cells in early-reacting tissues. This phenomenon may be related to differences in the repair capacity and proliferation kinetics of the two populations.

The mammalian central nervous system has been shown to be exceptionally vulnerable to damage by neutrons.[17] For most other biological systems, in both laboratory animals and man, clinical RBEs of approximately 3.0 are found when the relatively high energy neutron beam used at Fermilab is compared to conventionally fractionated photons.[8,11,13] Animal experiments on irradiation of the brain and spinal cord[17] have shown the corresponding RBE in the central nervous system to be between 4 and 5. Early clinical studies on the risk of encephalopathy[4,10,12] and myelopathy[4,10,12] in patients treated for tumors of the head and neck showed that the susceptibility of the CNS to neutron injury also held true in

the clinical context. Further experiments on primates[9] confirmed the exceptional vulnerability of the spinal cord to neutron irradiation in the clinical dose range.

When clinical studies were commenced at Fermilab in 1976, we were aware of this constraint on spinal cord tolerance and adopted a treatment planning policy whereby the maximum spinal cord dose would not exceed 12.5 Gy (with the exception of 5 patients who received between 13 and 16.7 Gy because of tumor location). Since doses of 50 Gy of conventionally fractionated photons are known to be well tolerated, or associated with a minimal risk of spinal cord injury, the limit of 12.5 Gy with neutrons assumed an RBE of 4.0 for our beam. This requirement imposes a severe constraint on treatment planning for head and neck cancer.[3] The tumor doses required are generally of the order of 22 Gy, which may have to be delivered both to the primary tumor and to involved lymph nodes in the anterior and occasionally posterior neck (Fig. 1). It is often extremely difficult to irradiate this volume uniformly while ensuring that the spinal cord remains outside the 57% contour.

It is important that the maximal safe limit for neutron irradiation of the human spinal cord be established accurately. The onset of myelopathy in long term survivors treated with neutrons must be avoided at all costs. On the other hand, to impose such severe constraints on the spinal cord dose may compromise the treatment plan, thereby leading to death from tumor

recurrence, is equally undesirable. In this paper we report our experience of 76 patients who survived 1 year or more following treatment of head, neck or thoracic tumors with neutrons. Since no radiation myelopathy has been noted in this series, we believe we may confidently define a lower limit for the spinal cord tolerance dose.

METHODS AND MATERIALS

The patient population studied had received fast neutron radiation therapy for the treatment of various tumors of the head, neck and thoracic regions at the Fermilab Neutron Therapy Facility.[1,5] This facility provides a fixed horizontal beam of neutrons generated by the p(66)Be(49) reaction, appropriately collimated and delivered in an isocentric mode to patients immobilized in a sitting or standing position in a rotating fixture. Beam characteristics and depth dose distribution are similar to 6-8 MeV X-rays.[2,15,16] Seventy-six patients treated between September 1976 and November 1982, who survived 1 year or more after treatment, and in whom the spinal cord was directly within the geometric edges of one or more beams, were selected to evaluate the risk of spinal cord injury with neutron beam irradiation. Seventy patients had been treated for head and neck tumors and 6 patients were treated for thoracic malignancies. The ages ranged between 13 and 86 years (Fig. 2). Mixed beam (photon plus neutron) patients are not included in this study. We also

reviewed the records of patients who did not survive one year, to be sure that we were not overlooking any cases of early myelopathy. No myelitis was reported in these patients.

Seventy patients had received definitive neutron radiation therapy as the primary treatment for a biopsy-proven malignancy. Three patients were treated for recurrence after single or multiple radical surgeries, 2 patients for recurrence after photon irradiation, and 1 patient after failure of a chemotherapy regimen.

Planning X-ray films and contour information taken in the treatment position after immobilization were available for analysis. Depending on the anatomy of the spinal cord, and its position relative to the target volume, one or more contours were taken, always including one at the level of the isocenter. Treatment plans were individualized on the basis of clinical and radiographic evidence of tumor extent. Typically, multiple fields were used to achieve uniform irradiation of the target volume (Fig. 1), generally keeping the entire spinal cord dose below the tolerance limit, believed to be 12.5 Gy, although this could not always be achieved. Several patients did, in fact, receive higher cord doses. The length of spinal cord irradiated varied from 5 to 18 cm (Fig. 3). Treatments were given 2 or 3 times a week for a total period of 3 to 8 weeks. The fraction size ranged from 0.80 to 2.85 Gy with total target absorbed doses between 12 and 27 Gy.

In this study, spinal cord doses are expressed in terms of the "central cord dose", that is, the absorbed dose at the point where an isodose line in the principal plane of the beam intersects the central axis of the spinal cord. Those values are plotted in Fig. 4. With the dose distributions generally used in this series of patients, the dose across the spinal cord is relatively uniform (see, for example, Fig. 1) and maximum cord doses are generally of the order of 9% greater than the nominal central cord doses described (Fig. 5).

RESULTS

No myelopathy was observed in this series of 76 patients (Table 1). There was no evidence of unequivocal Lhermitte's syndrome in any of these patients. On careful questioning, six patients admitted to experiencing a mild transient paresthesia in one extremity, unrelated to movement of the neck.

The relevant time-dose data are plotted in Fig. 6 in which the total central cord dose is related to the overall treatment time (closed circles). An analysis relating cord-dose to fraction number gave an essentially identical diagram (not shown) since time and fractions are strongly correlated. In many patients the initial treatment was given through wide fields which included the spinal cord and was followed by a "boost" to a smaller volume, generally excluding the cord. In these patients, the cord dose

received in the initial phase of treatment is plotted separately in the same figure (open circles); these patients provide lower levels for the doses tolerated over the shorter treatment times.

For comparison, published reports on neutron induced myelopathy from Hammersmith Hospital[4] (H), from the MANTA project[12] (M) and the University of Washington in Seattle[10] (S) are also shown in Fig. 6. Inspection of the figure suggests that a straight line, corresponding to a cord dose of 13 Gy can be drawn, below which no myelopathy is observed. The best-fitting discriminant line should probably be horizontal, or almost so, to minimize the number of non-myelopathy points above the line. This confirms the concept that with neutrons, the slope of the Strandquist line is probably little greater than zero.[7] The onset of symptomatic transient paresthesia appears to be sporadic and unrelated to dose or time factors.

DISCUSSION

Studies with low-LET radiation, in both animal experiments[14] and human dose-time analysis,[6] have shown that the target cells in the irradiated mammalian central nervous system have a high capacity for repair of sublethal damage, with the result that these tissues are able to tolerate relatively high doses of conventionally fractionated radiations. This capacity for repair would be less evident with high-LET radiation. Consequently, a

relatively high RBE for late effects in the central nervous system compared to other organs or tissues would be anticipated. In addition to this biological factor, the elemental compositions and mechanisms of energy transfer from the neutron beam to the spinal cord and surrounding tissues may contribute to more severe reactions with neutrons. These factors could combine to produce a significantly higher effective RBE for the tissues of the spinal cord if computed isodoses, which assume uniformity in chemical composition of soft tissues, are used to calculate cord doses. It is clearly this effective RBE which must be used as a conservative estimate of spinal cord tolerance in clinical practice. Under these circumstances the present study shows that with the high energy neutrons used in the Fermilab facility, the RBE for tolerance of human spinal cord does not exceed 4.0 when compared to conventionally fractionated high energy photons.

Since photon doses as high as 50 Gy delivered in 25 fractions over 5 weeks (33 days) are well tolerated,[18] neutron doses of the order of 12.5 Gy may be taken as a safe tolerance limit with a vanishingly small risk of spinal cord injury. This limit has been shown to be true for a reduced fractionation, since most of our patients were treated with no more than 13 fractions twice a week. It would be expected that this tolerance limit would be little changed by variation in fractionation with overall treatment times between 4 and 6 weeks. A review of published data (Table 2) also shows that no instance of myelopathy was observed unless at least

some portion of the spinal cord received a dose greater than 12 Gy.

Published Data. All published reports[4,10,12] on neutron-related myelopathy are consequent upon delivery of neutron doses well above 12 Gy. The beam quality in these cases differed from that of the present study. Neutron energies were lower using the deuteron (16, 22 and 35 MeV)-beryllium reaction. With the neutron spectra produced in this way, RBEs would be expected to be higher and consequently cord damage might be observed at lower doses than the tolerance limit for the high energy Fermilab beam. The lowest dose reported to have been associated with myelopathy was in the Hammersmith series, in which one patient developed spinal cord injury following a cord dose of 9 Gy.[4] However, further dosimetric analysis showed that the maximum cord dose was over 12 Gy in this patient. Since the newer neutron therapy cyclotrons currently under construction in the US and Europe all have high energies (45 to 60 MeV protons and Be-targets), tolerance limits in these facilities are likely to be closer to the Fermilab experience than to any of the older data.

Fermilab Data. Six patients in this series reported questionable transient paresthesia. Symptoms first appeared between 3 and 8 months following neutron irradiation, and were observed on only one occasion in each patient. These patients described a tingling sensation in one extremity, unrelated to flexure of the neck. One

patient had hyperreflexia and clonus. The symptoms, reported at one or two follow-up visits, were transient, did not progress, and resolved spontaneously in all cases (Table 3). The central cord dose ranged from 6.0 to 15.0 neutron Gy. The onset of paresthesia is not obviously related to dose.

One patient treated for a cervical chordoma received 14.7 Gy as a central cord dose, had no further treatment for one year and then received an additional 4.5 Gy to an adjacent portion of her spinal cord when she was retreated with neutrons. A narrow overlapping zone may have received a total dose of 19 Gy. She has survived over one year since the second course and has had no evidence of CNS injury.

We conclude from our observations that an assumed RBE of 4.0 and a conservative tolerance limit of 12.5 Gy provides a realistic constraint on treatment planning where the spinal cord receives a substantial neutron dose, and does not greatly depend on the fractionation scheme used. This limit is associated with a minimal risk of spinal cord injury and corresponds to doses of 50 Gy delivered with conventionally fractionated photon radiotherapy. However, there are clinical contingencies where somewhat higher doses might be delivered to the spinal cord, taking a calculated risk of myelopathy in situations where control of the tumor would be unlikely with lower doses. With photon therapy, a dose of 60 Gy (in 30 fractions over 6 weeks) to a short

segment of spinal cord might be given under these circumstances. The concomitant risk of myelopathy, which probably lies between 5 and 10%, might be considered acceptable if this is the only way in which a reasonable prospect of tumor control can be achieved. By the same reasoning, the dose of neutrons carrying a corresponding calculated risk of myelopathy would be of the order of 15 Gy with the high energy beam currently available. It is for this reason that 5 of our patients received neutron doses of this order. All have remained free of spinal cord injury at the 2 year follow-up date and 2 have been followed for 5 years without any problems related to the spinal cord.

CONCLUSIONS

It was our purpose to review all available data in our records to better establish the tolerance of the human spinal cord to therapeutic doses of neutrons. It has been shown that,

1. No myelopathy was observed in 46 patients receiving central cord doses in excess of 10 Gy in 8 to 23 fractions over 4-8 weeks;

2. Similarly, 9 patients who received central cord doses of 12 Gy or more showed no evidence of spinal cord injury;

3. Central cord doses between 14.6 and 16.7 neutron Gy (12-23 fractions over 6-8 weeks) have been tolerated (in 5 patients)

without evidence of myelitis;

4. A review of the literature suggests that cord doses of 15 Gy or more are hazardous and associated with a significant risk of myelopathy; maximum cord doses of 13 Gy or less are probably safe with high energy neutrons.

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Table 1

Neutrons 66 MeV - Fermilab - 1984

Survival (Years)	Patients at Risk	Central Cord Dose >10 Gy	>11 Gy	>12 Gy	>13 Gy	Response
1	76	46	33	9	5	no myelitis
2	33	18	13	5	3	" "
3	20	10	7	3	2	" "
4	10	5	4	3	2	" "
5	8	5	4	3	2	" "

Table 2

Incidence of Myelopathy with Neutron Beam Therapy.

Author and Institution	Equipment	Central Cord Dose	Patients with cord damage/Patients evaluated
M. Catterall Hammersmith Hospital London, UK	16 MeV d→Be cyclotron	11 - 16 Gy	5/?
G. Laramore University of Washington Seattle, WA	22 MeV d→Be cyclotron	Approx. 15 Gy	5/10
R. Ornitz MANTA Washington DC	35 MeV d→Be cyclotron	15 - 16 Gy	4/40
Fermilab Batavia, IL	66 MeV p→Be Linear accelerator	6 - 17 Gy	0/76

Table 3

Questionable Transient Paresthesia

Tumor Site	Central Cord Dose (Gy)	Maximum Cord Dose (Gy)	Field Length (cm)	Survival in months/status
Neck	6.0	9.3	15	57.0 mo/alive
Hypopharynx	15.0	18.0	10	84.0 mo/alive
Oropharynx	14.6	15.7	10	72.0 mo/alive
Supraglottic Larynx	9.6	10.1	10	42.0 mo/alive
Oropharynx	11.0	12.0	12	19.5 mo/dead
Lung	7.4	7.7	15	14.75 mo/dead

Figure Captions

1. Typical neutron treatment plan for head and neck primary with one involved node. The first 44% of the dose is given through the opposing fields 1 and 2. The next 33% is given with 3 and 4. The last 22% is given with boost field 5. For 22.5 Gy target absorbed dose, minimum target dose is 20 Gy, contralateral neck receives 15 Gy for microscopic disease and the entire cord dose is less than 12.5 Gy.

2. Age distribution of 76 patients under study.

3. Distribution of field sizes used for treatment. Where a reduced boost field was used, that size is given here.

4. Distribution of doses to the center of the spinal cord in the principal plane of the beam for the 76 patients under study.

5. Distribution of maximum doses received by the spinal cord in the principal plane of the beam for the patients under study.

6. Scatter plot of central cord dose versus treatment time for the patients under study •, with initial "wide

field" values (e.g., fields 1 & 2 in Fig. 1) illustrated for 28 of those patients ○ . Also included are some literature reported cases of myelopathy following neutron irradiation H,[4] M,[12] S.[10]

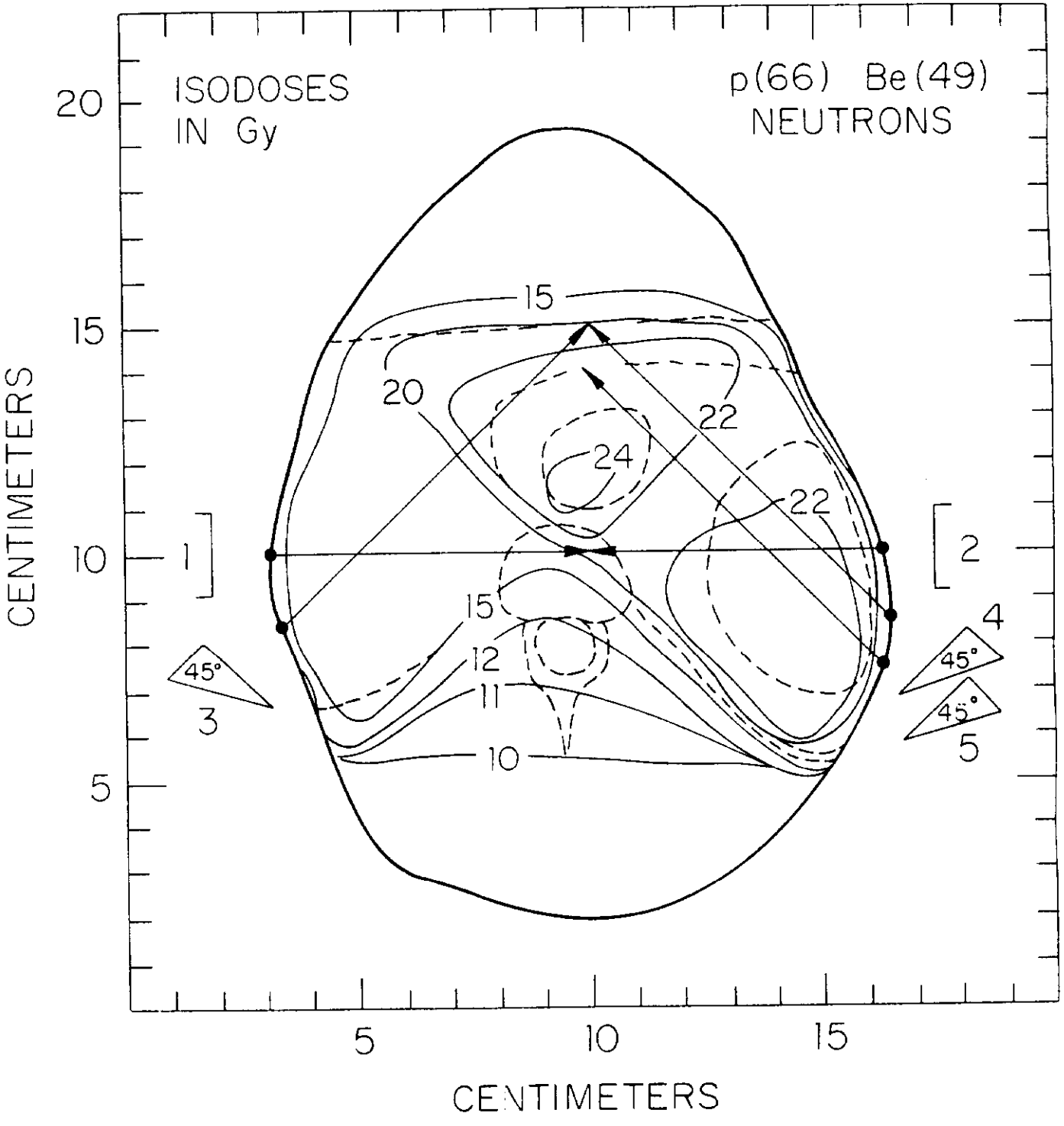
ISODOSES
IN Gy
p(66) Be(49)
NEUTRONS
15
20
22
24
22
15
12
11
10
1
2
3
4
5
45°
45°
45°
CENTIMETERS
CENTIMETERS
5
10
15
5
10
15
20

Figure 1

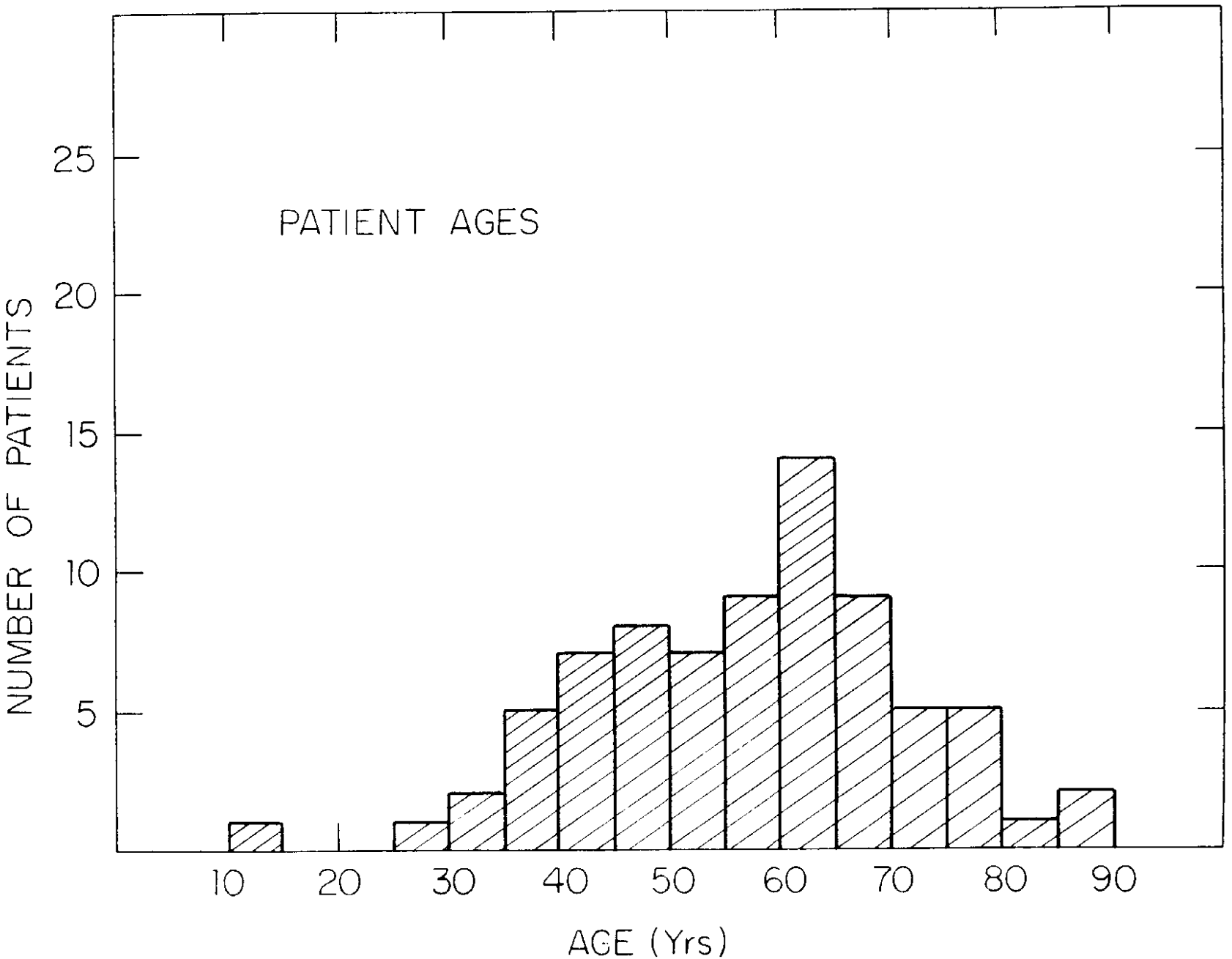
PATIENT AGES
NUMBER OF PATIENTS
25
20
15
10
5
10
20
30
40
50
60
70
80
90
AGE (Yrs)

Figure 2

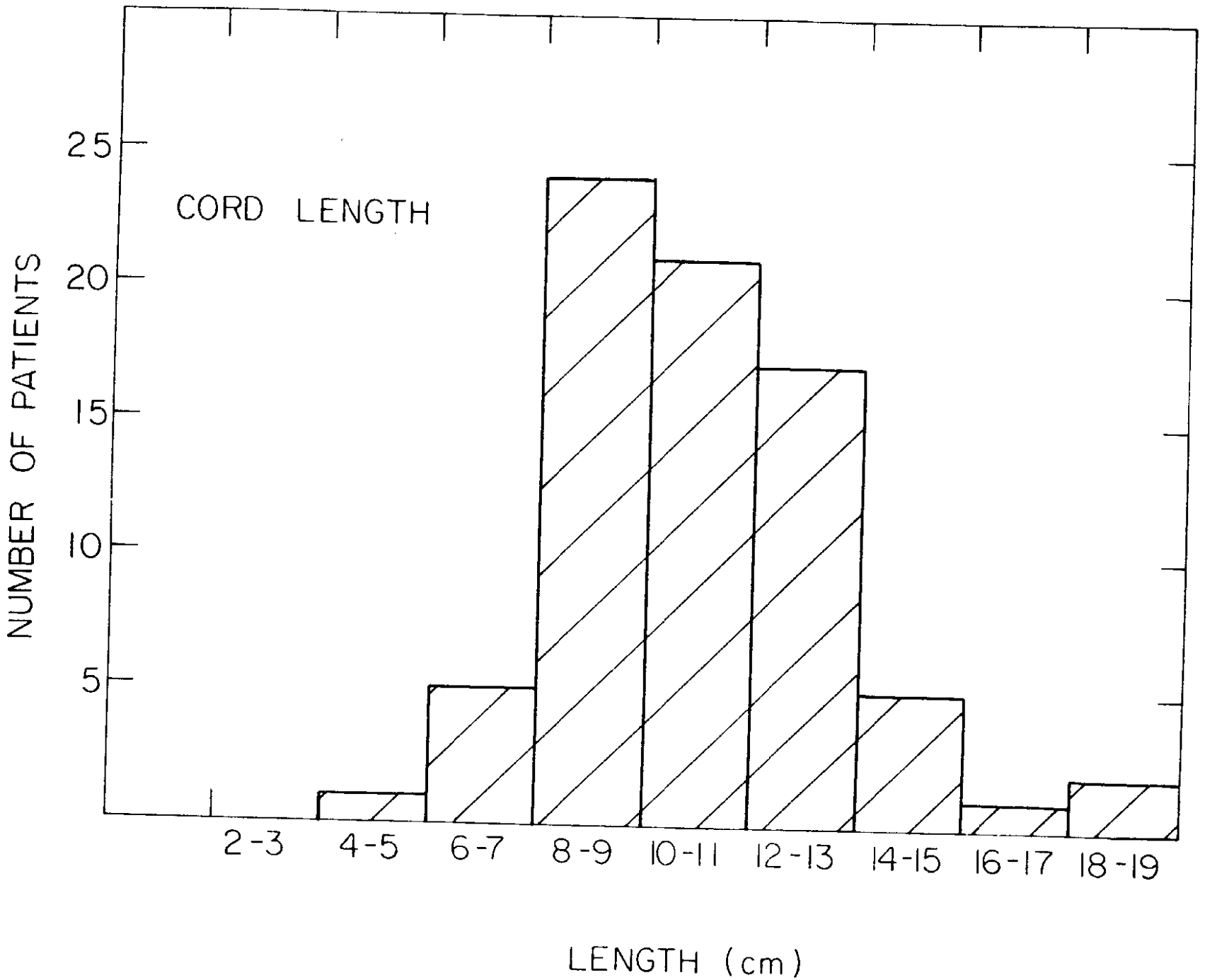
CORD LENGTH
NUMBER OF PATIENTS
25
20
15
10
5
2-3
4-5
6-7
8-9
10-11
12-13
14-15
16-17
18-19
LENGTH (cm)

Figure 3

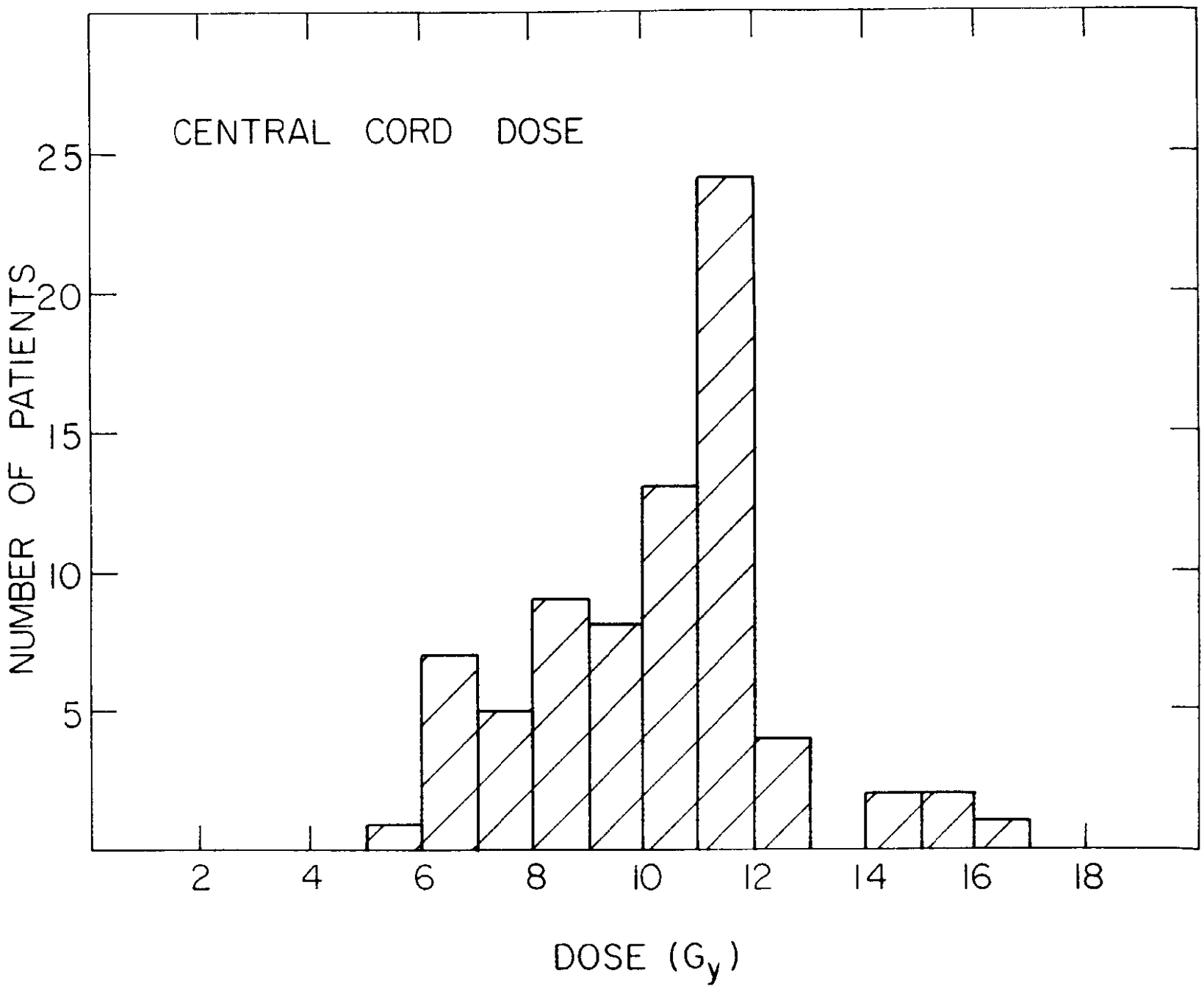
CENTRAL CORD DOSE
NUMBER OF PATIENTS
25
20
15
10
5
2
4
6
8
10
12
14
16
18
DOSE (Gy)

Figure 4

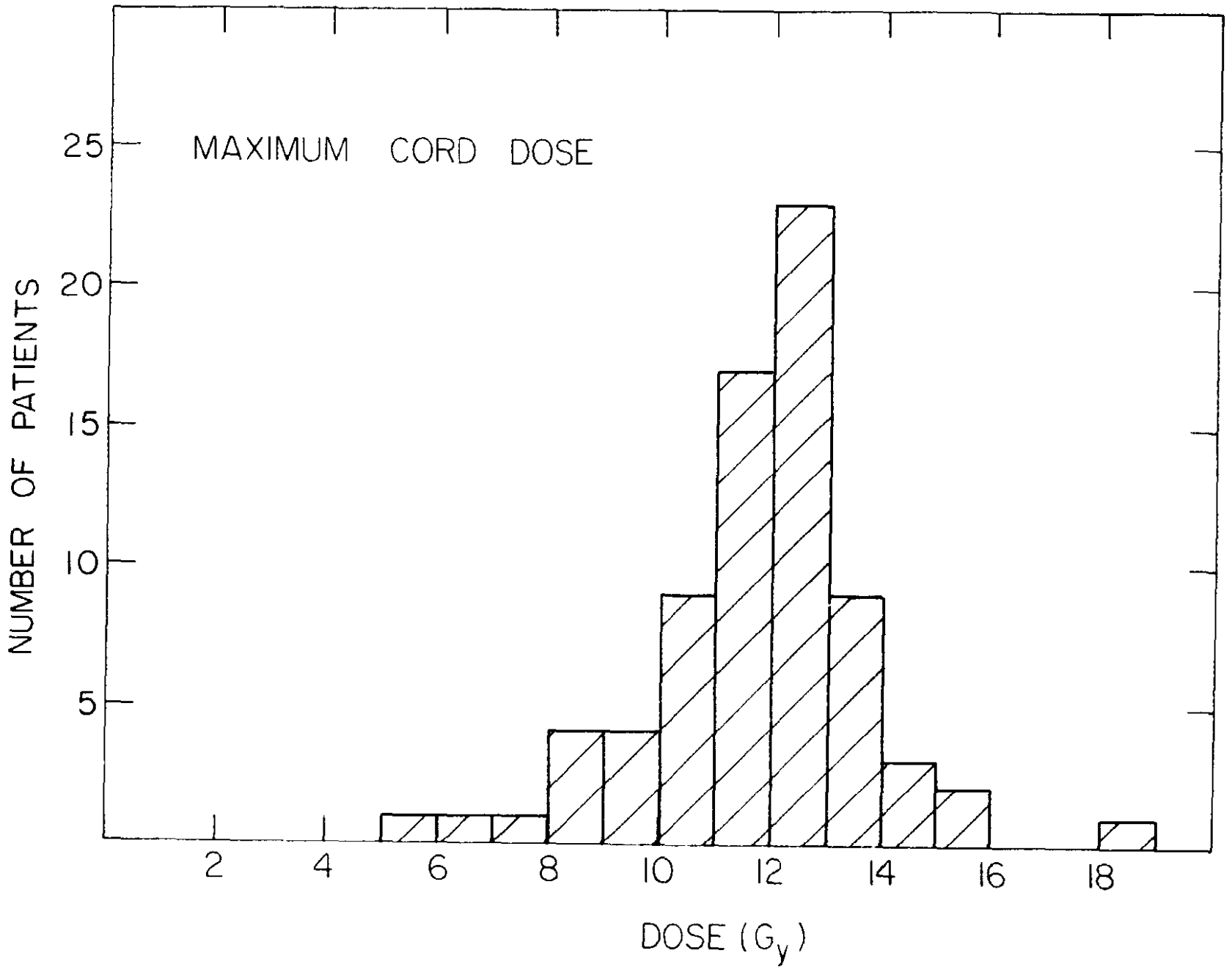
MAXIMUM CORD DOSE
NUMBER OF PATIENTS
25
20
15
10
5
2
4
6
8
10
12
14
16
18
DOSE (Gy)

Figure 5

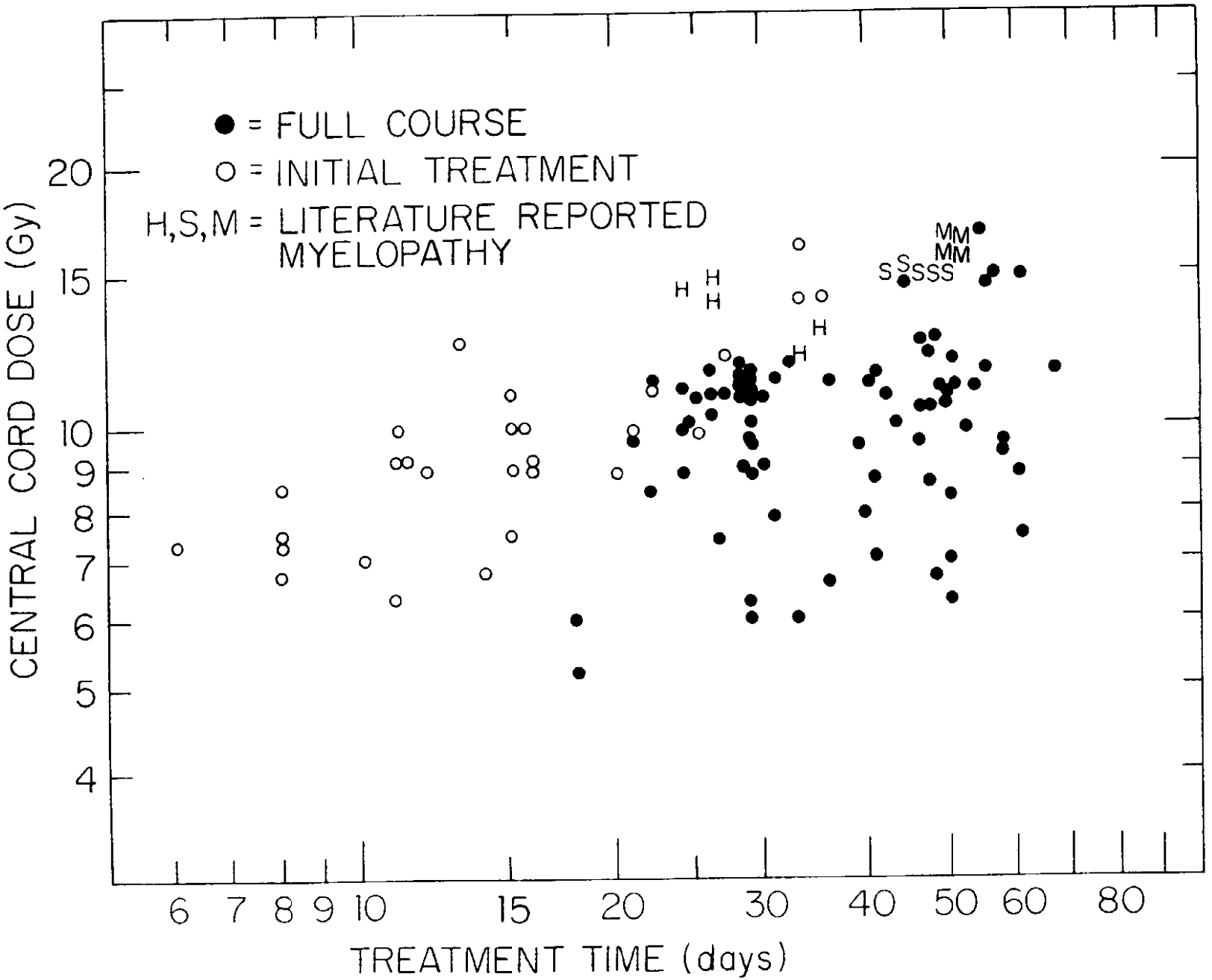
● = FULL COURSE
○ = INITIAL TREATMENT
H,S,M = LITERATURE REPORTED MYELOPATHY
CENTRAL CORD DOSE (Gy)
20
15
10
9
8
7
6
5
4
6
7
8
9
10
15
20
30
40
50
60
80
TREATMENT TIME (days)

Figure 6