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DOSE EFFECT RELATIONSHIPS IN CERVICAL AND THORACIC RADIATION MYELOPATHIES

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In 1968 ZEMAN reported that the latency period for necroses following a single dose of irradiation was strictly time dependent. Since then this question has been repeatedly discussed in connection with radiation myelopathies in man. Current experience implies that no clear negative relationship between the dose and latency period after fractionated radiation exists (FRANKE 1973). This also holds true for animal experiments in which a latency period of four to five months cannot be further reduced under fractionated radiation (VAN DER KOGEL & BARENDSEN 1974).

On the other hand radiation myelopathies have been reported that prove fatal after a short latency period and a progressive course versus other conditions with a long interval and a long survival time. These suggest that the latency period and the extent of the lesions, i.e. the survival time, may depend upon the irradiation doses (latency period—survival time—relationship). Thus, HUNG (1968) found an average latency period of 18.6 months among the lethal cases of his series versus an average of 25.4 months latency, in contrast to ATKINS & TRETTER (1966) as well as JELLINGER & STURM (1971) who failed to detect any correlation between the latency period, the severity of clinical symptoms and signs and survival time or any dependence of these factors on the radiation dose. This in turn does not corroborate the result of GÄNSHIRT (1978). In a relatively homogeneous group of patients with complications subsequent to radiation therapy of the lymphatic system, he found a rough relationship between the dose and the severity of neurologic syndromes. Evidently the question of dose effect relationships remains a matter of considerable controversy.

Material and Methods

The present series and well-documented cases in the literature were entered into a latency catamnesis diagram to describe the course types (Figure) and classified according to cervical and thoracic radiation myelopathies. Lumbar or thoracolumbar myelopathies were excluded from the series because they are rare and often incorrectly classified as to the exact localisation, the so-called amyotrophic type being not a myelopathy at all, but rather a peripheral neuropathy (HOLDORFF 1979). Only those cases in the literature were considered that provided a precise and extensive documentation of the neurologic status and the course of the patients.

The cases of radiation therapy of the lymphatic system and myelopathies following two radiation cycles were treated separately. The observation after irradiation of the lymph nodes was classified together with the cervical radiation myelopathies, as the classification was based on neurologic findings; autopsy results not always being available. Occasionally thoracically located spinal necroses could not be entirely ruled out.

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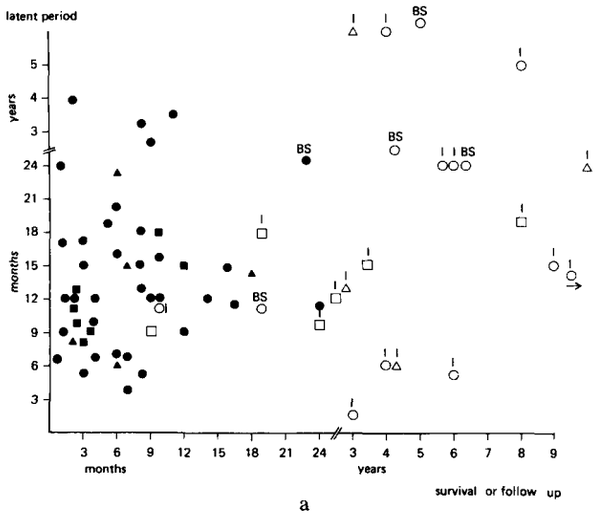
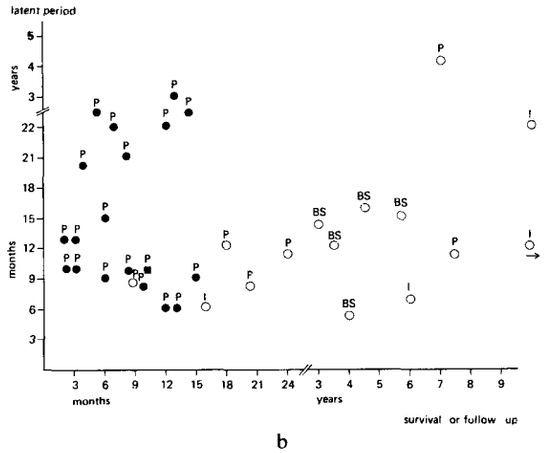


a

Radiation myelopathies. a) Cervical. b) Thoracic. Living (○), deceased (●). Living (□), deceased (■) after 2 series of irradiation. Living (△), deceased (▲) after mantle field irradiation.



b

Paraplegia (P). Brown-Séquard (BS). Incomplete transverse syndrome (I).

Due to the large field of irradiation the question of the exact location of the necrosis remains open. The neurologic status indicates a level which does not necessarily correspond to the level of the spinal necroses. These may at times extend higher into the cervical region even though neurologic signs indicate the thoracic region of the spinal cord (CASTAIGNE et coll. 1970).

These difficulties of the localization do not as a rule occur in those radiation myelopathies following a small irradiated volume because in these cases irradiation field and spinal cord lesions coincide.

The appearance of the first neurologic symptoms of radiation myelopathy marked the beginning of the survival time or follow-up period. The terminal stages of the neurologic disease were designated by letters; this was not possible in cases of cervical radiation myelopathies with a fatal outcome, for which frequently no documentation of the neurologic findings at the terminal stage was available but only a status taken days or weeks before the final phase. One can only speculate that, in the final phase, transverse syndromes with partial involvement of the upper extremities developed into upper tetraplegic transverse syndromes. Paraplegias in cases of thoracic radiation myelopathies were on the other hand documented reliably.

Though the relationship between the latency period and the survival or follow-up period and in turn their dependence upon the radiation dose were of primary interest. The extent to which various neurologic criteria and the segmental localization of the spinal cord lesion influenced course and prognosis was also analyzed.

Results

The Figure does not allow a generalization and postulation of a linear relationship between the latency period and the survival time though such a relationship might be considered for some of the thoracic paraplegia cases. On the other hand it is crucial for the clinical course whether the radiation myelopathy progresses to a complete transverse syndrome, i.e. tetraplegia due to cervical lesions and to paraplegia because of thoracic ones. The fatal outcome results in the majority of such cases within 10 to 18 months after the appearance of the first symptoms (black symbols in the Figure). The comparison of the latency periods of those patients who died early with those who died later—after 18 months—and with the survivors yields no statistically significant difference in the Wilcoxon test. This applies to both the cervical and the thoracic radiation myelopathies. Only those cases were considered in which the possible cause of death was a radiation myelopathy or a secondary effect such as respiratory insufficiency with pneumonia, hypotension or pulmonary embolism. The surviving patients present mainly with incomplete spinal syndromes, either as Brown-Séquard syndromes or as incomplete transverse syndromes; these allowing a more

Table 1

Nominal standard dose in cervical radiation myelopathies

Fatal course			Non-fatal course		
NSD	Authors	Case No.	NSD	Authors	Case No.
14.2	SEITZ & KALM (1961)	3	11.3	ZEMAN & SHIDNIA (1976)	
14.2	MARTY & MINCKLER (1973)		11.3	JELLINGER & STURM (1971)	10
14.3	JELLINGER & STURM (1971)	12	12.9	GLANZMAN et coll. (1976)	5
14.3	PALMER (1972)	7	$\bar{x}$=14.6	JELLINGER & STURM (1971)	7
14.8	PALMER (1972)	2			
17.2	JELLINGER & STURM (1971)	3	15.5	SOLHEIM (1971)	3
18.1	LECHEVALIER et coll. (1973)	5	17.3	SOLHEIM (1971)	4
$\bar{x}$=18.1	LECHEVALIER et coll. (1973)	1	20.8	SOLHEIM (1971)	2
			Median 14.6		
18.6	JELLINGER & STURM (1971)	8			
19.1	JELLINGER STURM (1971)	4			
19.8	HOLDORFF (1979)	1			
20.1	JELLINGER & STURM (1971)	9			
21.9	JELLINGER & STURM (1971)	2			
22.5	JELLINGER STURM (1971)	11			
23.8	LECHEVALIER et coll. (1973)	2			
Median 18.1					

favorable prognosis quoad vitam. Yet both short and long latency periods occur and the series allows no correlation between the latency period and dose or further modalities of irradiation, such as two radiation series within a few months and high radiation volumes in cases of radiation therapy of the lymphatic system.

No significant difference was found in the prognosis between lesions of the upper and lower cervical segments.

For 36 fatal cervical radiation myelopathies, a median survival time of 6.5 months is calculated ranging from $\frac{3}{4}$ to 16.5 months, and for 18 fatal thoracic radiation myelopathies, a median survival time of 7.5 months ranging from 2 to 15 months is found. For the six fatal cases following two consecutive irradiation cycles performed within a few months, the median survival time lay at 3 (2–10) months and is particularly short.

Under the hypothesis that fatal and non-fatal courses or complete and incomplete transverse syndromes were the result of different radiation doses, a possible dose effect relationship was sought. Only those cases could be referred to in which the nominal standard dose (NSD) was either specified or could be calculated. The NSD value was calculated according to the formula of Ellis:

$$NSD = D \times N^{-0.24} \times T^{-0.11}$$

As the dose D was expressed in Gy the NSD value was expressed in 100 ret. If the median spinal dose is calculated for those patients who died within the first 18 months and for the group of survivors (Table 1), NSD of 18.1 (median value) is yielded for the 15 fatal cervical cases and a NSD of 14.6 for the 7 survivors with incomplete transverse syndromes. The difference is significant at the 10 per cent level.

Almost identical NSD values of about 15.4 are calculated for the fatal and non-fatal thoracic cases. However, if the complete and incomplete thoracic transverse syndromes are separated (Table 2), a NSD of 16.9 is found in the first group of 14 cases and a NSD of 15.3 for the second group of 6 cases. This difference is statistically significant at the 5 per cent level of the Wilcoxon test. For radiation myelopathies following irradiation of the lymphatic system (Table 3), a median NSD value of 15.2 is calculated for complete transverse syndromes in 4 cases and a NSD value of 13.2 for 5 incomplete transverse syndromes. The difference is again significant at the 5 per cent level.

If incomplete transverse syndromes following upper mantle field irradiation (Table 3) are compared with incomplete thoracic transverse syndromes

Table 2

Nominal standard dose in thoracic radiation myelopathies

Complete transverse syndrome			Incomplete transverse syndrome		
NSD	Authors	Case No.	NSD	Authors	Case No.
14.5	LOCKSMITH & POWERS (1968)	1	14.5	LOCKSMITH & POWERS (1968)	2
15	PALMER (1972)	5	14.5	LOCKSMITH & POWERS (1968)	4
15	PALMER (1972)	6	15	LOCKSMITH & POWERS (1968)	5
15.3	PHILLIPS & BUSCHKE (1969)	1			
16.1	PALMER (1972)	1	15.5	PALMER (1972)	3
16.7	LOCKSMITH & POWERS (1968)	3	16	GLANZMANN et coll. (1976)	3
16.7	LOCKSMITH & POWERS (1968)	6	16.1	ATKINS & TRETTER (1966)	13
17	ATKINS & TRETTER (1966)	12	Median 15.3		
17.5	GLANZMANN et coll. (1976)	2			
17.6	COY et coll. (1969)	1			
17.9	COY et coll. (1969)	2			
18.1	COY et coll. (1969)	3			
19.7	PHILLIPS & BUSCHKE (1969)	3			
19.9	PHILLIPS & BUSCHKE (1969)	2			
Median 16.9					

Table 3

Nominal standard dose in radiation myelopathies after upper mantle field irradiation

Complete transverse syndrome			Incomplete transverse syndrome		
NSD	Authors	Case No.	NSD	Authors	Case No.
13.4	GLANZMAN et coll. (1976)	5	12.5	GÄNSHIRT (1975)	2
14.9	GÄNSHIRT (1975)	6	13	GLANZMANN et coll. (1976)	4
15.4	GÄNSHIRT (1975)	9	13.2	GÄNSHIRT (1975)	4
16.2	GÄNSHIRT (1975)	3	13.4	HOLDORFF (1979)	5
			13.7	GÄNSHIRT (1975)	7
Median 15.2			Median 13.2		

(Table 2), a median NSD value of 13.2 and 15.3, respectively, is found. These values differ significantly at the 5 per cent level. Despite the small number of cases in both groups the statistical comparison is justifiable, because all NSD values in the group following upper mantle field irradiation are smaller than the smallest value of the other group with thoracic radiation myelopathies. A part of the results is compiled in Table 4.

Discussion

The present results indicate that the fatal outcome of many servical and thoracic radiation myelopathies occurs within 18 months of the appearance of the first neurologic symptoms, i.e. when they develop into a complete transverse syndrome, while incomplete transverse syndromes are consistent with a longer survival time.

An attempt to distinguish upper and lower cervical radiation myelopathies by morphologic and neurologic criteria does not yield any clinically useful differences in the course of the ultimate fatal cases. The median survival time of 6.5 months for 36 fatal cervical myelopathies does not essentially differ either from the median survival time of 7.5 months for 18 fatal thoracic myelopathies. Nevertheless, for the course and the prognosis the

Table 4

Nominal standard dose in radiation myelopathies

Cervical		Thoracic		After upper mantle field irradiation	
Fatal	18.1	Complete	16.9	Complete	15.2
Non-fatal	14.6	Incomplete	15.3	Incomplete	13.2
$2\alpha<10\%$		$2\alpha<5\%$		$2\alpha<5\%$	

importance of the segmental localization of spinal necroses should not be ignored.

It is known that in cases of traumatic transverse lesions the mortality rate depends upon the segmental localization of the spinal lesion and increases particularly for lesions in the upper cervical part of the medulla, i.e. C1–C4, mainly due to acute respiratory paralysis (MESARD et coll. 1978). In the cases of cervical radiation myelopathy it is difficult to distinguish different courses of upper and lower cervical radiation myelopathy because of the inhomogeneous distribution of the necroses over a large segment of the spinal cord.

Furthermore, the present analysis proceeded on the assumption that the dose causing spinal cord necrosis would have to differ for complete and incomplete transverse syndromes. This assumption was confirmed statistically for those cases with a known NSD. The median spinal necrosis dose mentioned is not identical with the threshold of tolerance, which lies well below the range of necrosis doses. Nevertheless, the spinal cord necrosis dose of incomplete radiogenic transverse syndromes comes closest to the threshold tolerance because it represents a submaximum overdosage and not a maximum one as in the case of complete transverse syndromes. The scattering range of NSD is, as expected, small (Tables 2, 3). For this reason incomplete transverse syndromes are best suited for determining the threshold of tolerance. This is only possible when the clinical course may be observed for a sufficiently long period of time so that a later progression to a complete transverse syndrome may be excluded. According to this principle a median spinal necrosis dose of NSD 15.3 and 13.2 could be determined for the incomplete thoracic radiation myelopathies and for those following lymph node irradiation, respectively.

This division into complete and incomplete transverse syndromes cannot be applied to cases of cervical radiation myelopathy because, in many cases of the literature, incomplete cervical transverse syndromes were described with an early fatal outcome where, presumably, the complete tetraplegic transverse syndrome in the final phase was not recorded. On the other hand all surviving patients presented with an incomplete transverse syndrome either unilaterally along the lines of the Brown-Séquard syndrome or as a bilateral incomplete transverse syndrome. Therefore, it is suggested for cervical radiation myelopathies that the course criterion fatal corresponds to complete and non-fatal to incomplete transverse syndromes. A mean spinal necrosis dose of NSD 14.6 was determined for non-fatal incomplete cervical radiation myelopathies.

These criteria for neurologic differentiation have up to now not been applied in the reports on radiation myelopathy risk. According to compilations of data the critical range in which radiation myelopathies may occur fluctuates between NSD values of 10 and 20 (FRANKE) but most often lies above 15 (PHILLIPS & BUSCHKE 1969, GLANZMANN et coll. 1976). For reasons of safety a tolerance dose 10 per cent lower than this is applied to the cervical part of the medulla (GLANZMANN et coll.). In contrast ABBATUCCI et coll. (1978) consider a dose of 50 Gy (25 fractionations in 35 days=NSD 15.7) to be safe if a longitudinal segment of the cervical region of the spinal cord covering no more than three to five vertebrae is irradiated. For the thoracic region of the spinal cord, WARA et coll. (1975) calculated a 50 per cent incidence rate of approximately NSD 16, while RHEINHOLD et coll. (1976) determined one of NSD 19.8 which, however, is probably far too high. This error may be due to the fact that, because of the average latency period of 18 months, many cases are not recorded in morbidity investigations of radiation myelopathy because of premature death due to the primary disease (FRANKE).

Tolerance calculations do not fully appreciate the

volume factor although in principle its significance has long been known. As early as 1950 BODEN found that a radiation myelopathy occurred, if a longitudinal spinal cord segment of more than 20 cm was irradiated with an otherwise well-tolerated dose. ATKINS & TRETTER, ZEMAN & SHIDNIA and ABBATUCCI et coll. also stressed the significance of the volume factor. It is also of importance when considering the craniospinal irradiation of children. The present results emphasize that also an increased risk of radiation myelopathy is involved in high-volume irradiation of the lymphatic system in cases of Hodgkin's disease and other forms of malignant lymphoreticular disease. Incomplete transverse syndromes after a mantle field irradiation of this type (Table 3) and incomplete thoracic radiation myelopathies after low-volume irradiation (Table 2) show a significant difference in their median spinal necrosis dose (5 per cent level). This statistical comparison is justifiable in spite of the small number of cases, because all NSD values of the group after mantle field irradiation are lower than the lowest values of the other group with thoracic radiation myelopathies. Thus, it can be stated that the limit of tolerance of the spinal cord for mantle field irradiations is lower and a safety limit of NSD 12 may be assumed. These results indicate that it would be logical to introduce the volume factor to the conventional NSD formula (GREMMEL & WENDHAUSEN 1977), especially in view of the radiation myelopathy risk.

SUMMARY

The course and prognosis of radiation myelopathies are determined by 3 factors: the segmental (vertical) location of the lesion, the extent of the transverse syndrome (complete or incomplete) and the radiation dose. The median spinal dose in cervical radiation myelopathies with fatal outcome was higher than in survivals with an incomplete transverse syndrome. In thoracic radiation myelopathies a dose difference between complete and incomplete transverse syndromes could be found as well. Incomplete transverse syndromes as submaximum radiation injuries are more suitable for the determination of the spinal tolerance dose than complete transverse syndromes. The lowest threshold could be stated for cases following high-volume irradiation of the lymphatic system.

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