TOLERANCE DOSE OF THE SPINAL CORD ON RADIATION MYELOPATHY

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ABSTRACT

Radiation myelopathy has developed in 9 cases among irradiated patients as a side effect following radiotherapy for malignant tumors. The dose to the spinal cord was 5,000-10,000 rads, the over all treatment time 42-71 days. Several causative factors of the radiation myelopathy were picked up.

The degree of radiation influences in the spinal cord seem to be time-dose dependent, as reported by Boden and Pallis. A recommended tolerance dose to spinal cord was over 4,000 rads and over 5,000 rads according to Tsuya's and Friedman's reports respectively and an NSD* of 1,300 rets and 1,500 rets was recommended by Maier and Phillips respectively. From the data presented it is apparent that degree of occurrence of radiation myelopathy depends greatly on fractionation and irradiation dose. When the patients are treated in more than 21 fractions at a daily dose of 200 rads and the dose to the spinal cord irradiated is more than 5,000 rads, it can be considered to be the critical level for radiation myelopathy.

INTRODUCTION

Recent development of radiotherapy for malignant tumors coupled with the life prolongation of the tumor patients has focused a light on radiation myelopathy seen as a side effect of this therapy.

Statistics made in foreign lands shows that this disease occurs at the incidence rate of several per cent. In Japan until present radiation myelopathy has been considered as a rare complication, but now it tends to be increasing. Warren^{1,2} reported that the central nervous system was not affected at all for its

* NSD=Nominal Standard Dose by Ellis²⁶

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

DN: Total dose in rads

N : Number of fraction

T : Overall treatment time

low radiosensitivity by the dose of ordinary level irradiated to malignant tumors. However, the further studies revealed that the central nervous system might be one of the tissues that have high radiosensitivity to irradiation in the functional level. (Tsuya).^{3,4,5}

Ahlbom⁷ (1941) referred to this disease first, and there are a moderate number of reported cases in the literature. According to these reports it was concluded that the factors causing radiation myelopathy were closely related with the irradiation dose, the overall treatment time, the number of fractions, the radiation energy, the length of the spinal cord included in the field of irradiation, and the individual tolerance differences.

The present paper describes an analysis of nine cases of radiation myelopathy observed in this hospital which received radiotherapy for malignant tumors

Table 1
Radiation myelopathy cases in our hospital

Case	Sex	Age	Diagnosis	Radiation energy	Treatment of portals	Field Size/cm	Location of spinal treated	Tumor dose /rad	Over-all time /days	No. of fractionation
1	M	68	Ca. of the lung	6 MeV X	2	8×12	T ₂ -T ₈	7,000	42	35
2	F	56	Malig. struma	Co-60	1	6×6	C ₅ -T ₁	6,350	64	39
3	M	67	Ca. of the lung	6 MeV X	2	11.8×7.2	T ₄ -T ₈	12,000	71	57
4	F	40	Ca. of the gingiva	6 MeV X	2	7×7	C ₁ -C ₆	7,000	46	35
5	M	45	Ca. of the pharynx	200 KV X	2	8×10	C ₁ -C ₆	10,300	69	47
6	M	39	Mediastin tumor	6 MeV X	2	11.2×14	T ₂ -T ₈	7,200	45	34
7	F	46	Malig. struma	Co-60	2	6×8	C ₅ -T ₂	10,200	68	46
8	F	29	Ca. of the breast	6 MeV X	1	5×15	T ₂ -T ₉	6,900	50	32
9	M	29	Mediastinal tumor	6 MeV X	2	14.5×10.5	C ₆ -T ₃	8,000	48	40

during the period of 1966–1972 and is intended to supply further clinical information in the hope that it will help more precisely to define the radiosensitivity of the spinal cord.

MATERIALS AND METHOD

During the past six years (1966–1972) nine patients of radiation myelopathy were observed in our hospital as a result of radiotherapy for malignant tumors. These nine patients were selected from about 600 patients with malignant tumor who had received radiotherapy, indicating that the incidence rate of this disease was about 1.5 per cent.

The clinical manifestations of the myelopathy grouped them into the chronic

Dose to spinal cord /rad	N. S. D. /rets	Latent interval	Myelopathy type	Clinical findings	Myelography	Protein in liquor	Statur & survival
7,000	1,970	6 mo	transient	Lehrmitte's sign	—	—	Dead 4.5 y
5,600	1,470	6 mo	progressive	Brown-Sequard Syndrome (below T ₅)	Normal	13mg/dl	Alive 8 mo
10,000	2,380	18 mo	progressive	Brown-Sequard Syndrome (below T ₇)	Normal	125mg/dl	Dead 8 mo
6,200	1,730	8 mo	progressive	Paresthesia right hand & leg	Normal	46mg/dl	Dead 10 mo
9,000	2,220	38 mo	progressive	Paresthesia both legs	Normal	80mg/dl	Dead 3 y
7,000	2,100	3 mo	transient	Lehrmitte's sign	—	—	Alive 2 y
7,000	1,970	12 mo	progressive	Brown-Sequard Syndrome (below T ₅)	Normal	Normal	Dead 3 y
5,600	1,590	26 mo	progressive	Brown-Sequard Syndrome (below T ₅)	Adhesion	24mg/dl	Dead 18 mo
8,000	2,150	6 mo	progressive	Paresthesia right hand & both legs	Normal	35mg/dl	Alive 4.5 y

progressive type (6 cases) and the transient type (3 cases). The diagnosis of these 9 cases were cancer of the lung (2 cases), malignant struma (2 cases), mediastinal tumor (2 cases), cancer of the breast (1 case) cancer of the pharynx (1 case) and cancer of the gingiva (1 case).

From the viewpoint of radiation energy, 6 cases were irradiated with super-voltage x-rays of 6 MeV (NEC), 2 cases received gamma rays with Co-60 teletherapy units and 1 case received grid therapy of conventional x-rays. The x-ray treatment was given through two field portals with the exception of two cases of breast cancer and struma. The daily dose was 200 rads, weekly dose 1,000–1,200 rads and total dose 6,000–12,000 rads which were sufficient to eradicate malignant tumors. The number of fractions ranged 32–57 and overall treatment time 42–71 days.

Irradiation field was from 6×8 cm to 11.2×14 cm. The smaller field served for tumor of head and neck, the larger field served for mediastinal tumors and cancer of the lung. The dose irradiated to the spinal cord was from 5,600 rads to 10,000 rads (Table 1).

In the present series the latent period from the completion of therapy to the

Table 2
Incidence rate of radiation myelopathy

Author	Tumor patients for examination	Patients with radiation myelopathy	%
Ahlbom (1941)	235 cases	4 cases	1.7
Greenfield (1948)	180 cases	3 cases	1.7
Boden (1948)	161 cases	10 cases	6.2
Jacobsson ²⁴⁾ (1951)	322 cases	13 cases	4
Friedman (1954)	100 cases	10 cases	10
Dynes (1960)	800 cases	10 cases	1.3
Parker (1963)	125 cases	6 cases	5
Vaeth (1964)	322 cases	3 cases	0.9
Locksmith (1968)	48 cases	6 cases	12.5
Philips (1969)	350 cases	3 cases	0.9
Tan ²⁵⁾ (1969)	22 cases	3 cases	13.3
Maier (1969)	343 cases	15 cases	4.5
Egawa (1970)	60 cases	4 cases	6.7

earliest symptoms was from 3 months to 38 months. It was within one year for 6 cases and over one year for 3 cases, the average being 14 months. Tsuya *et al's* observation that the latent period was, in general, shorter in the transient type than in the chronic progressive type coincides with our findings that the latent period in the transient type was 3–6 months which was shorter than in the chronic type (Table 3).

Table 3
Radiation myelopathy and its latent period

Author	Cases	Latent period
Greenfield (1948)	3 cases	3.5–5 months
Boden (1948)	10 cases	1–15 months
Boden (1950)	3 cases	12–17 months
Itabashi (1957) ²¹⁾	2 cases	4.5–15 months
Dynes (1960)	10 cases	7–50 months
Pallis (1961)	5 cases	7–18 months
Atkins (1966) ²²⁾	14 cases	6–29 months
Kristensson (1967) ¹³⁾	5 cases	7–40 months
Regan (1968) ⁹⁾	10 cases	5–26 months
Locksmith (1968)	6 cases	12–35 months
Phillips (1969)	3 cases	10–13 months
Egawa (1970)	5 cases	50 days–10 months

CLINICAL FEATURES

The transient type of this series showed a Lehrmitte's sign. Symptoms of the chronic progressive type were accompanied by sensory and motor deficits. A Brown-Séquard syndrome was manifested in 5 cases out of 9. The onset presented often with a paresthesia tingling, and an abnormal sensation of upper or lower extremities. Pain radiating down the leg was another complaint. These initial symptoms were accompanied by sensory changes with loss in pain and temperature perception on one side of the body and subsequently on the other. Dysfunction of bladder and rectum was evident, often together with complete paralysis seen at the segment of the spinal cord irradiated. There were several cases, how-

ever, of incomplete paralysis. A Brown-Séquard syndrome was observed in 5 cases out of 7 of the chronic type, and 2 cases manifested incomplete paralysis. The transient type underwent spontaneous resolution of symptoms within 5–6 months after the onset in 2 cases, while no relief was observed in the chronic progressive type.

The radiation myelopathy is referred as a dangerous sequela where death rate within 2 years is very high and the patients die rather from infections via respiratory and urinary tracts due to paralysis than from malignant tumors. In the present series fatal outcome was observed in 5 cases out of 9. Three died from radiation myelopathy and 2 from other fatal causes.

Clinical laboratory examinations revealed the following features.

1. There was no destructed image in the x-ray photographs of the spine.
2. The spinal fluid was normal in all cases with the exception of slight increase of the concentration of protein (13–125 mg/dl).
3. Contrary to the previous findings that myelogram examination demonstrated no difficulty in passage, our 2 cases showed compression and congestion due to adhesions.
4. Tendon reflex (P.S.R.) was increased in all cases and abnormal in 7 cases.

Criteria for the diagnosis of radiation myelopathy

The precise diagnosis of radiation myelopathy is often difficult to determine because of its long latent interval between completion of radiotherapy and onset of symptoms and also because the disease which are most likely to lead to it are malignant tumors that induce paralysis due to metastasis to spine, thus requiring the appropriate procedure to avoid misinterpretation. We decided several preliminary criteria for diagnosing radiation myelopathy as follows;

1. The spinal cord is included in the field of irradiation.
2. The latent period from completion of radiotherapy to the earliest symptoms ranges from several months to three years.
3. Development of a neurological lesion is confined within spinal cord segments submitted to irradiation or below these.
4. Although consideration must be also given to the field of irradiation, the irradiation dose, the number of fractions, and the overall treatment time, the dose to the spinal cord should be 4,000–5,000 rads or more.
5. The symptoms are manifested by sensory and motor deficits that gradually develop, and *Lehrmitte's* sign and a Brown-Séquard syndrome are observed in some cases. No relief of symptoms is observed with the

exception of the transient type.

6. Examinations of the spinal fluid reveal either an almost normal condition or a slight increase of protein.
7. In general difficulty in passage is not observed in myelography.
8. Metastases to the spine or carcinomatous neuropathy should be excluded from the diagnosis.

Although there are many reports in which the critical dose to induce the irradiation myelopathy is less than 4,000 rads, it is a common observation that the critical dose is 4,000–5,000 rads or more in a daily dose of 200 rads and in many fractions.

Pathology

Pathological examinations in this series showed that the main lesions were limited to the field included in the irradiation. Spinal cord showed degeneration, necrosis, and atrophy. In the blood vessel there were chronic changes including hypertrophy of the intima, fibrosis of the wall and hyalin degeneration. The lesions of the spinal cord were marked particularly in white substances, in which demyelination was evident at anterior, posterior or left lateral columns. In comparison to white substances grey substances underwent relatively fair damage but some tissues often showed a destruction. Preliminary autopsy performed in 2 cases of this series will be illustrated in case reports. Photograph 1 taken for these cases demonstrated a clear demyelination at bilateral and posterior columns, hypertrophy of intima of blood vessel, and increased glia cells. These findings are to be noted in contrast to Jones *et al's* findings that there was no demonstrable lesions by autopsy performed on the patients with the transient type after the relief of the symptoms.

Illustrative case reports

One case of transient type and one of progressive type of illustrious radiation myelopathy are reported in this paper.

Case 1: a 68-year-old male was admitted to our hospital in 1966. A chest roentgenogram showed a large mass in the right lung and he was diagnosed as cancer of the lung. At a daily dose of 200 rads he received a tumor dose of 7,000 rads in 42 days, in 35 fractions on 6 MeV Linac x-rays through 8×12 cm opposing anterior and posterior fields. He did well during 6 months after completion of therapy, but on May 1968 he noted paresthesia at lower extremities together

with Lehrmitte's sign manifested by motor deficit in the left lower extremity. The disease was not further aggravated and underwent spontaneous resolution of symptoms within 5–6 months. Next 3 years he did quite well without recurrence of cancer of the lung nor metastasis of lung tumors and free from symptoms of radiation myelopathy up to May, 1972, when he observed blood in sputum and a chest roentgenogram showed a mass ascribed to recurrent tumor in the right lower lung. He had a fatal outcome in spite of radiotherapy. Clinically this case is grouped as a transient type of radiation myelopathy. The latent period from completion of therapy to onset of the disease was about 6 months and the dose to the spinal cord was 7,000 rads.

Autopsy showed the lesions ascribed to recurrence of lung carcinoma manifested by demyelination in posterior and bilateral columns, vitreous hypertrophy in intima of capillary blood vessel and increased glia cells. This case is an example which has different pattern from Jones *et al*'s findings that in a patient of transient type the spinal cord irradiated had not underwent lesions.

Case 2: a 57-year-old male was admitted to our hospital. A chest roentgenogram showed a mass ascribed to tumors in the right lung and he was diagnosed as cancer. Operation was impossible because of his heart disease. He was then referred for radiotherapy. He was treated with 6 MeV Linac x-rays through opposing anterior and posterior portals measuring 11.8×7.2 cm and in 71 days, in 57 fractions, and in a daily dose of 200 rads, he received a

Fig. 1 (case 1) Photo-micrograph of section through the Spinal cord. Destruction of both lateral columns.

Fig. 2 (case 1) Spinal cord showing fibrosis, in places hyalin, thickening of the vessel walls, destruction of white matter and cellular infiltration.

tumor dose of 12,000 rads. The dose to the spinal cord might be about 10,000 rads. Tumor shadow on the picture disappeared completely and the prognosis was better till 18 months after the therapy, when he became aware of loss of sensory and temperature perception. The myelopathy was progressing and Brown-Séquard syndrome developed at a level lower than left T₇. The examination of spinal fluid revealed an increase of the concentration of protein (125 mg/dl). Myelography showed no difficulty in passage. He was grouped as a progressive type of radiation myelopathy and despite further treatment he had a fatal outcome 8 months after the onset. Autopsy showed a wide demyelination spreading over posterior to lateral columns of the spinal cord irradiated to the T₇-T₉ level.

DISCUSSION

For the relation between the irradiation dose and radiation myelopathy, Boden^{10,11} (1948) established a tolerance dose of 3,500 rads in 17 days with larger fields and a tolerance dose of 4,500 rads to the spinal cord in 17 days with smaller fields and it must be not excess 2,000 rads daily. Pallis *et al* established a tolerance dose 20 per cent lower than those which Boden suggested for both large and small fields. These tolerance doses are actually considered to be the indicator when we determine the irradiation dose and overall treatment time (Figs. 3 and 4). Boden *et al* presented several cases of radiation myelopathy subsequent to 1,800

rads and 2,040 rads in single treatment, where in 10 cases out of 13 the dose to the spinal cord was less than 4,000 rads. If radiation myelopathy develops upon such a small dose of irradiation, radiotherapy of malignant tumors would require a severe control.

Fig. 3 Radiation myelopathy (Dose-time relationship).

Fig. 4 Radiation myelopathy (Dose-time relationship).

Classical work from Greenfield⁹ (1948) and to Kaneko⁶ (1972) made on the radiation myelopathy is referred in Table 4 in which the dose to the spinal cord is shown. This indicates that the dose required to develop the disease is in the level higher than 4,000 rads according to the authors including Greenfield,

Table 4
Radiation myelopathy and the dose to the spinal cord

Author	Cases of radiation myelopathy	Dose to the spinal cord
Greenfield (1948)	3 cases	4,454—6,480 R
Boden (1948) Boden (1950)	13 cases	{ Single 2,200—2,250 R Fractionation 3,000—5,250 R
Dynes (1960)	10 cases	2,500—6,000 R
Pallis (1961)	5 cases	2,850—8,700 R
Kozuka ²³⁾ (1964)	1 case	7,000 R
Kristensson (1967)	5 cases	4,000—5,100 R
Locksmith (1968)	6 cases	3,870—4,370 R
Regan (1968)	10 cases	4,000—6,900 rads
Phillips (1969)	3 cases	3,300—7,000 rads
Egawa (1970)	5 cases	6,000—9,969 R
Tsuya (1970)	2 cases	4,000—6,000 rads
Kaneko (1972)	3 cases	4,320—8,066 rads

Table 5
Incidence rate of radiation myelopathy relative to the dose irradiated to the spinal cord

	Dose	Cases	%	%	%
1	— 2,000 rad	5 cases	9%	20/53 38%	28/53 52%
2	2,100— 3,000 rad	4 "	8%		
3	3,100— 4,000 rad	11 "	20%		
4	4,100— 5,000 rad	8 "	15%	33/53 62%	25/53 47%
5	5,100— 6,000 rad	5 "	9%		
6	6,100— 7,000 rad	10 "	19%		
7	7,100— 8,000 rad	4 "	8%		
8	8,100— 9,000 rad	2 "	5%		
9	9,100—10,000 rad	4 "	8%		
	Total	53 cases			

Kristenson,¹³ Reagan⁸ and Egawa. Some of the patients included in the study of Dynes,¹⁵ Phillips,¹⁶ Pallis¹² developed the disease at a dose less than 4,000 rads. Atkins²² reported that radiation myelopathy developed in 4 patients even at a dose of 1,900 rads.

The dose of irradiation thus varied over a wide range. The further analysis was made on the causative factor for this variance. The relation between dose to the spinal cord and incidence rate of the radiation myelopathy in 53 cases included in the study of Nagase, Tsuya, Egawa,¹⁴ Kaneko, Atkins, Phillips, Pallis, and Locksmith¹⁷ is shown in Table 5. The table shows that it can not be determined only by dose to the spinal cord what is the factor causing radiation myelopathy. However, when the number of fractions is taken into account, the onset of radiation myelopathy relates to the number of fractions. In the number of fractions fewer than 10 the myelopathy develops even with irradiation dose of 2,000–3,000 rads to the spinal cord.

An increase of the number of fractions to 11–20 is followed by the onset of the disease at a dose of 3,000–5,000 rads, and the dose over 5,000 rads is the critical dose level when the number of fractions was over 21 (Table 6).

Table 6
*Number of fractions and incidence rate of radiation
myelopathy relative to the dose to the spinal cord*

	Dose to spinal cord (rad)	The number of fraction		
		Below 10	11–20	Over 21
1	— 2,000	4	0	1
2	2,100— 3,000	4	0	0
3	3,100— 4,000	2	8	0
4	4,100— 5,000	1	6	1
5	5,100— 6,000	0	1	5
6	6,100— 7,000	0	0	10
7	7,100— 8,000	0	0	4
8	8,100— 9,000	0	0	2
9	9,100—10,000	0	0	4
	Total cases	11 cases	15 cases	27 cases

These results indicate that when a large tumor dose of irradiation for malig-

nant tumor at one treatment is given, the myelopathy develops even in the relatively small dose to the spinal cord. But 5,000 rads is considered to be the critical dose when ordinary irradiation is performed in such a way that a patient receives a daily dose of 200 rads, and it is necessary to consider NSD (total dose in rads, number of fraction and over all treatment time) by Ellis. The table 7 shows relationship between radiation myelopathy and rets by NSD.

Table 7
Relationship between 53 cases of radiation myelopathy and rets

NSD (rets)	CASE	%	NSD (rets)	CASE	%
1201-1300	1	2	1701-1800	3	6
1301-1400	3	6	1801-1900	4	7.5
1401-1500	6	11	1901-2000	12	23
1501-1600	7	13	2001-2100	4	7.5
1601-1700	5	9	2101-	8	15

SUMMARY

During the past 6 years (1966-1972), radiation myelopathy has developed in 9 patients among tumor patients as a side effect following radiotherapy for malignant tumors. The latent period was 3-38 months, the average being 14 months. The tumor dose was 6,000-12,000 rads, the overall treatment time 42-71 days, the dose to the spinal cord 5,000-10,000 rads. Several causative factors of the radiation myelopathy were picked up.

The degree of radiation influences in the spinal cord seem to be time-dose dependent, as reported by Boden and Pallis. A recommended tolerance dose to the spinal cord was over 4,000 rads and over 5,000 rads according to Tsuya's¹⁹ and Friedman's²⁰ reports respectively and an NSD²⁶ of 1,300 rets and 1,500 rets was recommended by Maier¹⁸ and Phillips respectively. From the data presented it is apparent that the degree of occurrence of radiation myelopathy depends greatly on fractionation and irradiation dose. When the patients are treated in more than 21 fractions at a daily dose of 200 rads and the dose to the spinal cord irradiated is more than 5,000 rads, it can be considered to be the critical level for radiation myelopathy, but from NSD by Ellis, tolerance dose of spinal cord is considered over 1,300~1,400 rets.

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