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NEUROLOGIC COMPLICATIONS AFTER IRRADIATION OF MALIGNANT TUMORS OF THE TESTIS

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Radiation-induced injury to nerve tissue unavoidably included in the irradiated areas during treatment of malignant tumors has been reported for both the peripheral (STOLL & ANDREWS 1966, SPIESS 1972) and the central nervous system.

Several clinical syndromes have been distinguished in connection with the lesions arising after irradiation of the cervicothoracic spinal cord. Transient radiation myelopathy (JONES 1964, BÆKMARK 1975) constitutes one group, with purely subjective symptoms in the form of paresthesias, often Lhermitte's sign, which disappear spontaneously within a few months. Another group is marked by irreversible, partial or complete transverse medullary lesions with spastic paresis, loss of sensibility, and bladder and rectum dysfunction. On the basis of the course, cases of acute radiation myelopathy have been described (BODEN 1948, PALLIS et coll. 1961), in which the symptoms reached their peak within a few days. However, such an acute course is rare; in most cases it is a question of a chronic progressive myelopathy developing over a period of months or years (REAGAN et coll. 1968, PALMER 1972).

In connection with irradiation of the lumbar spine in the treatment of malignant testicular tumors GREENFIELD & STARK (1948) used the designation postirradiation neuropathy to describe a syndrome with flaccid paresis in the lower extremities but without sensibility disturbance, and suggested that this could be the result of selective injury to anterior horn cells. Judging from the literature, this syndrome is uncommon. Fifteen such cases have been described (MAIER et coll. 1969).

Several authors have attempted to establish tolerance limits for the spinal cord at

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Table 1

Microscopic findings and clinical staging in the whole material and in patients alive at the follow-up

	Clinical stage	No. of patients	Alive at follow-up	Neurologic complications
Seminoma	I	56	50	3
	II	17	10	2
	III	2	0	0
Non-seminoma	I	47	32	6
	II	13	5	1
	III	16	1	0
Other tumors	I	3	1	0
	II	1	0	0
	III	1	0	0
Total		156	99	12

irradiation of the cervicothoracic spine (BODEN, PALLIS et coll., ATKINS & TRETTER 1966, PHILLIPS & BUSCHKE 1969, PALMER). Only a few authors (MAIER et coll., MAIER 1972) have estimated the dose-related risk of neurologic complications after irradiation of the lumbosacral spinal cord. In order to assess the frequency of such complications in relation to the radiation dose administered, a systematic clinical follow-up was therefore undertaken of all patients still alive at least 2 years after irradiation of the lumbosacral cord for a malignant testicular tumor.

Material and Treatment Method

The material consisted of all patients with malignant testicular tumors treated at this Department between February 1965 and October 1974. The period was chosen to ensure that all patients had survived for at least 2 years after completion of therapy. Of the total material of 156 patients, 99 were alive at the follow-up in October 1976. Ninety-five patients were examined clinically from the aspect of recurrences and neurologic complications. Four who did not come to the follow-up reported that they felt quite well and had no neurologic symptoms from the legs. The material was distributed according to the microscopic appearance and to the clinical staging which followed the method employed at the Walter Reed General Hospital (Table 1).

The median age was 39 years (range 18–81 years) for patients with seminoma and 28 years (range 5–71) for the non-seminoma group.

The treatment of malignant testicular tumors was uniform throughout the period covered by the investigation. After an ordinary orchidectomy, irradiation was given either as a therapeutic measure, to established lymph node metastases, or as a 'pro-

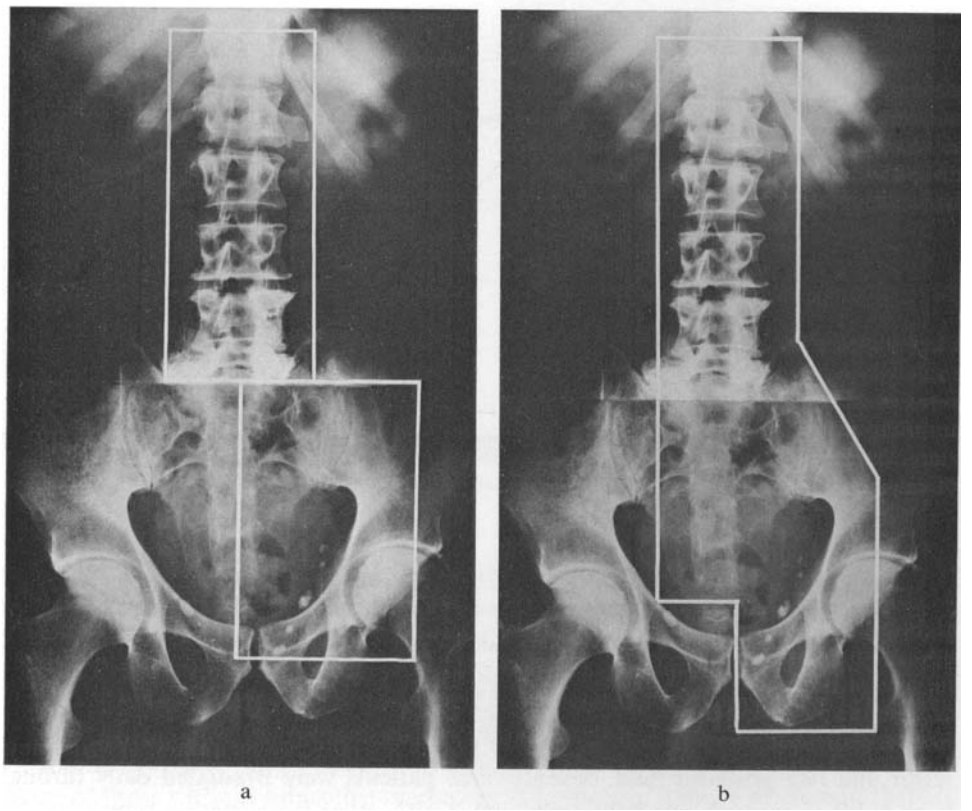

Fig. 1. Arrangement of iliac and para-aortic fields, with 2 opposing anteroposterior fields, for irradiation of malignant testicular tumors a) with ^{60}Co, b) with linear accelerator.

phylactic', to regional lymph nodes without known metastases. Bilateral lymphography from the foot was used in nearly all the patients. Biopsy of retroperitoneal lymph nodes was carried out in a few cases when metastases had been suggested at lymphography. None of the patients had undergone retroperitoneal aortic lymphadenodectomy.

The radiation fields included inguinal and iliac lymph nodes on the homolateral side, and the para-aortic lymph nodes bilaterally. The commonly used treatment field appears in Fig. 1. Its upper border was usually placed at the lower margin of the eleventh thoracic vertebra. Only in 6 of the patients followed up were the mediastinal and supraclavicular nodes also irradiated, because of metastases. All the fields were adjusted under fluoroscopy, with due consideration paid to lymphographic and urographic findings.

Of the total material of 156 patients, 57 (28 seminomas and 29 non-seminomas) received cobolt teletherapy, and 80 (46 seminomas, 31 non-seminomas, and 3 other tumor forms) were irradiated with a 6 MeV linear accelerator. Nineteen patients,

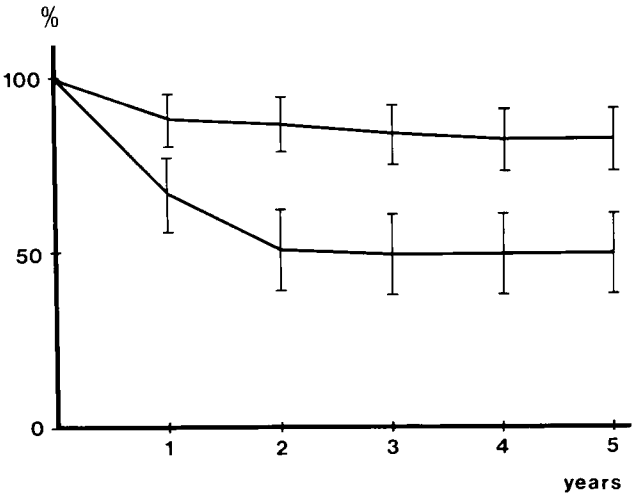

Fig. 2. Actuarial survival curves for 75 patients with seminoma (upper curve) and 76 non-seminoma patients (lower curve).

either because of age or widespread metastases, were given no irradiation or only palliative, pain-killing treatment. With cobolt teletherapy, the fields must be divided into two, due to the field length. The radiation was given daily, from the front and the back, alternately. Five patients were irradiated with a vertical beam and 52 with oblique beam in order to avoid overdosage (a 'hot spot') when the fields bordered on one another. Irradiation with the linear accelerator was directed through one anterior and one posterior field. Seventy-three patients were irradiated daily through both fields, 5 through one field daily, and 2 with other fractionation schedules. No correction for missing tissue was made in connection with the irradiation.

During the period under review, the central radiation dose, and thereby also the dose to the spinal canal, was 33 to 40 Gy/3 to 4 weeks for the seminomas and 45 to 57 Gy/4 to 6 weeks for the non-seminomas, with daily irradiations 5 to 6 times a week. This means that the CRE values (the cumulative radiation effect) ranged from 1 000 to 1 450 reu (radiation effect units) for the seminomas and from 1 450 to 1 900 reu for the non-seminomas.

Results

Ninety-nine of the 156 patients were alive at the time of the follow-up. The survival time for the material was calculated according to the actuarial method, and the cumulative survival rates for the 75 patients with seminoma and the 76 non-seminomas appear in Fig. 2. The cumulative 5-year survival for the seminomas was 82 per cent (73–91 %, 95 % confidence limits) and for the non-seminomas 49 per cent (38–65 %, 95 % confidence limits). According to the survival curves, nearly all the deaths occurred within the first two years after the irradiation. The observation time for patients alive at the time of the follow-up was 2 to 12 years, average 5.9 years. Only

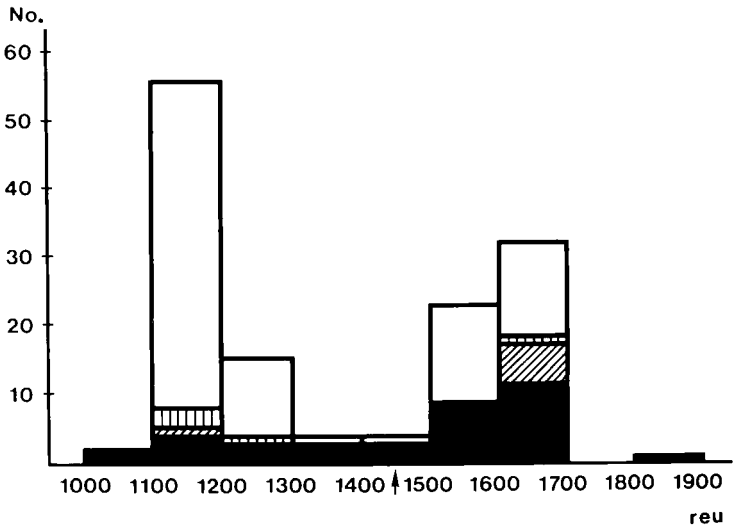

Fig. 3. Distribution of the whole material according to the radiation dose (reu). Patients dead at time of follow-up (black areas), alive without symptoms (white areas), with persisting neurologic symptoms (oblique shading), and with transient neurologic symptoms (vertical shading).

one of the patients in the follow-up had signs of a recurrence of the testicular tumor, 3 years after completion of radiation therapy. He had no neurologic symptoms.

Among the surviving 99 patients neurologic symptoms were present in 12 (12%). None of those without subjective symptoms had objective signs of neurologic deficits.

On the basis of the neurologic signs and symptoms present at the follow-up a number of clinical syndromes could be distinguished (Table 2). Five patients (5%, Cases 1–5) had purely subjective, mild discomfort in the form of paresthesias (4 instances) or a sensation of muscular weakness (1 instance). These symptoms disappeared after 3 to 6 months. In 2 patients (2%, Cases 6 and 7) the neurologic symptoms and signs were concentrated to the femoral nerve on the irradiated side; they were persistent, but caused little discomfort. In 5 patients (5%) the symptoms were considerable, causing disablement of varying degrees; 2 of them (Cases 8 and 9) had diffuse atrophy and paresis in one leg which in one instance necessitated a change of occupation from manual to office work, and 3 (Cases 10–12) had severe symptoms with marked, diffuse, symmetric, flaccid paresis in both legs, affecting especially the gluteal muscles, and the foot and toe extensors, and causing a waddling gait and drop foot. Only one of them (Case 12) had mild sensory symptoms in the form of hypoesthesia. The deep reflexes in the legs in these 3 patients were markedly weak, or absent, but the plantar, abdominal and cremasteric reflexes were normal. No signs of bladder and rectum dysfunction or impotence were observed. Myelography revealed arachnoiditis distal to the second lumbar vertebra in Case 10, but in Case 12 the arachnoid was normal. In Case 11, myelography was not performed as the pa-

Table 2

Survey of radiation treatment and clinical findings in 12 patients with neurologic complications

Case No.	Age (years)	Latent period (months)	CRE (reu)	Neurologic symptoms and signs	Clinical course	Observation time after irradiation (years)
1	30	3	1 670	Paresthesia both feet	Disappeared after 3 months	3½
2	38	2	1 182	Painful paresthesia L. leg	Disappeared after 3 months	5
3	30	2	1 146	Paresthesia both ankles	Disappeared after 6 months	8½
4	34	4	1 158	Paresthesia both legs	Disappeared after 6 months	7
5	42	9	1 250	Slight subjective weakness L. leg	Disappeared after 6 months	3
6	34	5	1 670	Slight weakness R. quadriceps. Hypoesthesia ant. aspect R. femur	Unchanged	2½
7	52	6	1 149	Hypoesthesia ant. aspect L. femur and inside of L. crus	Unchanged	3½
8	31	23	1 670	Moderate atrophy and paresis R. leg. Deep reflexes R. leg reduced	Unchanged	4
9	35	26	1 670	Moderate atrophy and flaccid paresis R. leg. Slight hypoesthesia inside R. crus. R. foot drop	Unchanged	6
10	33	12	1 670	Severe atrophy and flaccid paresis of the gluteal, femoral and ant. tibial muscles. Bilat. foot drop. Waddling gait	Unchanged	2
11	24	10	1 670	Marked bilat. atrophy and paresis of gluteal muscles, peroneal reflexes absent. Waddling gait	Gradual improvement	4½
12	25	14	1 608	Severe atrophy and paresis of both legs. Slight hypoesthesia R. ankle. Able to walk with crutches	Gradual worsening 5 years after onset of symptoms	8½

tient's symptoms had been receding over the past year, in that he had been able to discard his crutches. The symptoms had remained unchanged in Case 10, whereas in Case 12 they had become worse, being most severe 5 years after onset.

One of the patients who died had, 2 months after the irradiation, developed moderate paraparesis which remained unchanged until he died one year later, from peritonitis resulting from radiation necrosis of the colon. At autopsy, no signs of tumor recurrence, but marked fibrosis in the small pelvis were observed. This patient was not included among the cases with complications, as the spinal cord was not examined at autopsy and the possibility of metastases to the cord could therefore not be excluded. None of the other patients who had died developed neurologic deficits.

The latent period between completion of irradiation and the first neurologic symptoms was shorter, 2 to 9 months (average 4 months), in the group (Cases 1–5) with purely subjective and transient symptoms than in the group with persisting symptoms, in which it ranged from 5 to 26 months (average 14 months).

The irradiation of the above 12 patients with neurologic symptoms did not deviate from the standard procedures. Three patients received cobolt teletherapy through angled a.p. fields, one was treated with a linear accelerator through one field daily, and 8 with a linear accelerator through anterior and posterior fields daily. None of the patients with neurologic symptoms had received chemotherapy.

The relation between the radiation dose given and the degree of the neurologic symptoms appears in Fig. 2. There was a close connection between the severity of the symptoms and the dose, all patients with persisting pareses having received more than 1 600 reu. Only one patient with persisting symptoms, which however were purely sensory, had received a dose below this level. Of the 33 patients who received more than 1 600 reu, 20 were alive at the time of the follow-up; among these, 3 had paraparesis causing considerable walking difficulties and 2 paresis in one leg preventing heavy physical work.

In order to assess the significance of the length of the irradiated field the number of patients with paresis in the group with lengths shorter than 36 cm (2 among 43 cases) was compared with the number in the group with lengths of 36 cm or longer (4 of 50 cases). No significant difference was established (Fisher's exact text; $p = 0.43$).

Discussion

The neurologic complications after irradiation could in this series be divided into three groups. One group comprised 5 patients with purely subjective, mild symptoms of the type described by JONES. None of these patients had Lhermitte's sign, however. In the second group, with 2 patients, the symptoms could be ascribed to an isolated injury to the femoral nerve, as described by SPIESS. In accordance with SUNDERLAND's (1972) description, the symptoms in these patients with 'femoral neuropathy' were mainly sensory. They were constant, but not incapacitating.

In a third group, comprising 5 patients, the symptoms were consistent with the

clinical findings in the 'post-irradiation neuropathy' reported by GREENFIELD & STARK, but none of the patients had fasciculation, and the paresis was unilateral in 2 cases. A remarkable feature was that no bladder, rectum or sphincter disturbance or definite sensory loss existed in any of the cases. The pareses were especially marked in the gluteal muscles and in the extensors of the foot, which resulted in a characteristic, rolling gait and drop foot.

The neurologic signs of a persisting neuronal lesion, following irradiation, usually develop after a latent period; in the present series, this was 14 months on an average (range 5–26 months). Latent periods of up to 13 years have been mentioned in the literature, although a period longer than 2 years has been reported for only 6 out of 64 cases (PALLIS et coll., KRISTENSSON et coll. 1967, REAGAN et coll., SOLHEIM 1971, BURNS et coll. 1972, PALMER, GODWIN-AUSTEN et coll. 1975).

In most of the present patients with persisting lesions the symptoms remained unchanged, but in one case the pareses worsened appreciably 5 years after onset and in another an improvement took place 2 years after onset. Such an improvement is rare, but has been reported by SOLHEIM.

A number of factors are of significance in the definition of an irradiation treatment and an assessment of the possible injury to nerve tissue arising from this therapy. Thus, the following factors must be taken into consideration: total dose, dose per fraction, number of fractions, total treatment time, and field size. In most of the previous investigations to determine the connection between radiation dose and neurologic complications, dose-time curves have been compiled based on regression lines for the tumor dose in Gy/treatment time, in patients who developed symptoms (BODEN, PALLIS et coll., MAIER et coll.), or the tumor dose in Gy/number of fractions (ATKINS & TRETTER), both for short and for long fields. With these methods, only a few of the significant factors are included. ELLIS (1967, 1969) introduced the NSD value (nominal standard dose), which includes all the above-mentioned factors except field size. PHILLIPS & BUSCHKE used the NSD value when assessing the risk of radiation myelitis in the thoracic part of the spinal cord, and suggested a tolerance limit at 1 500 ret (radiation equivalent therapy). MAIER established a mean dose of 1 366 ret among 15 patients who developed myelitis after irradiation of malignant testicular tumors, and suggested a tolerance limit at 1 300 ret.

KIRK et coll. (1971) reworked Ellis's formula for the NSD, introducing instead the CRE value (cumulative radiation effect) to solve the problems connected with the concept of partial tolerance. These problems arise in connection with alteration of the fractionation, or gaps during therapy. The NSD value is directly comparable to the CRE values in the present series, if the fractionation was constant throughout the treatment period and no gaps existed. If intervals of more than 4 days occurred in the present series, a correction was made for the effect of the gaps on the CRE value (TURESSON & NOTTER). No signs of appreciable neurologic complications were observed in patients who had received less than 1 600 reu. On the other hand, 5 of 20 survivors given a dose of more than 1 600 reu had neurologic complications; 3 of

these (15 %) had severe disabling paraparesis, and 2 (10 %) moderately severe disabling paresis in one leg. Thus, the findings indicate that the tolerance limit for the spinal cord at the lumbar level lies at a value of not over 1 600 reu, which means a dose of 54.5 Gy over a period of 6 weeks with daily fractions 5 times a week.

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SUMMARY

Of 156 consecutive patients with malignant tumor of the testis 99 were alive two years after treatment. Of these, 12 had radiation-induced neurologic complications which, in 5 instances, consisted of persisting, wholly or partially disabling paresis in the lower limbs. Five had mild, transient symptoms and 2 had persisting symptoms which were not incapacitating. In all those with disabling symptoms the irradiation dose had been higher than 1 600 reu, corresponding to 54.5 Gy over 6 weeks with daily fractions 5 days a week.

ZUSAMMENFASSUNG

Zwei Jahre nach der Therapie waren 99 von 156 konsekutiven Patienten mit malignen Tumoren des Testis am Leben. Von diesen hatten 12 strahlenbedingte neurologische Komplikationen, welche in 5 Fällen aus totaler oder partieller invalidisierender Lähmung der unteren Extremitäten bestand. Fünf hatten lediglich subjektive geringe, vorübergehende Symptome und 2 hatten bestehende, doch nicht invalidisierende Symptome. Bei denjenigen welche invalidisierende Beschwerden hatten, war die Strahlendosis höher als 1 600 reu, entsprechend 54,5 Gy in 6 Wochen mit täglichen Fraktionen 5 Tage pro Woche.

RÉSUMÉ

Quatre vingt dix neuf malades sur une série consécutive de 156 cas de tumeur maligne du testicule étaient en vie 2 ans après le traitement. Parmi eux, 12 avaient des complications neurologiques dues aux radiations qui, dans 5 cas, consistaient en une parésie des membres inférieurs complètement ou partiellement invalidante. Cinq n'avaient que des symptômes purement subjectifs, légers et transitoires et deux avaient des signes fonctionnels ne causant pas d'inconfort. Chez tous les malades atteints de troubles invalidants, la dose d'irradiation avait été supérieure à 1 600 reu, correspondant à 54,5 Gy en 6 semaines avec des doses journalières 5 jours par semaine.

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