ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK, FINLAND, NORWAY AND SWEDEN

Vol. 9
Fasc. 3

THERAPY PHYSICS BIOLOGY

1970
June

RADIOSENSITIVITY OF MEDIASTINAL LYMPHOMAS IN HODGKIN'S DISEASE TREATED WITH SPLIT-COURSE RADIOTHERAPY

A retrospective study

by

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Radiotherapy has been the method of choice in the treatment of clinically local Hodgkin's disease since 1902, when PUSEY reported good results in malignant lymphomas. Several chemotherapeutics are now available but appear to be reserved mainly for patients in whom radiotherapy cannot be expected to produce the desired effect, especially if the disease is advanced. The belief that 'Hodgkin's disease is, in the end, always fatal' (PATERSON & PATERSON 1954) now seems to be giving way to the feeling that it is at least sometimes unicentric in origin and possibly curable by radiation treatment (KAPLAN 1962, 1966, EASSON & RUSSEL 1963, JELLIFFE 1965 and EASSON 1966), justifying irradiation of diseased tissues to adequate dose levels.

Opinions differ concerning the dose that should be given in the treatment of local Hodgkin's disease (Table 1). PITCOCK et coll. (1959) and FAYOS et coll. (1965) have reported longer survivals among patients treated with larger doses,

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and it has been demonstrated (JELLIFFE & THOMSON 1955, NOETZLI & SHELINE 1962, JELLIFFE 1965 and WESTLING 1965) that the number of recurrences after irradiation diminishes with increasing dose. KAPLAN (1966) presented a curve for different rates of recurrences at various dose intervals, based upon data from the literature which indicated that a dose of 4 000 rad over 4 weeks should be considered the 'tumoricidal' dose in Hodgkin's disease. Time versus dose diagrams for irradiated patients with Hodgkin's disease without and with local recurrences have been presented by SCOTT (1961), SCOTT & BRIZEL (1964), JELLIFFE (1965), FRIEDMAN et coll. (1967) and SEYDEL et coll. (1967). SCOTT (1961) gave a time-dose line that passed through 750 R in 0.45 days and 2 300 R in 20 days, the doses expressed representing 'the minimal tumor dose as estimated by the prescribing physician'. SCOTT & BRIZEL (1964) compared orthovoltage and supervoltage techniques. The doses had been calculated as 'minimal tumor dose in tissue roentgens along the central axis of the beam'. The patients received five treatments a week. The authors stated that successful treatment with the supervoltage technique required a significantly larger dose than did the orthovoltage technique. They also reported that the dose required for short treatment times is higher than might be expected. According to JELLIFFE (1965) considerable variations in the radiosensitivity of Hodgkin's disease exist, a view shared by FRIEDMAN et coll. (1967) who also thought that in one and the same patient the radiosensitivity of one lymph node group might vary from another one. Megavoltage radiotherapy required a larger dose than the orthovoltage technique. They recommended 3 500 rad over 4 weeks and gave the dose as 'a tumor dose' but failed to add a precise definition of the term. SEYDEL et coll. (1967) recommended a dose of 3 500 to 4 000 rad also over 4 weeks.

Special attention has been paid in certain reports to the irradiation of mediastinal lymphomas in Hodgkin's disease. HOHL et coll. (1951) pointed out that successful irradiation of the mediastinum often needs a longer period of treatment and thus a larger dose. They recommended target doses of between 3 000 and 4 000 rad. NICE & STENSTROM (1955) found that mediastinal involvement in Hodgkin's disease did not worsen the prognosis more than did involvement of any peripheral lymph node group. These authors recommended a minimum of 2 000 tissue roentgens to the tumour over 14 days. LEVITT (1959) recommended 2 500 R over 14 days. NOETZLI & SHELINE (1962) studied 11 recurrences in 22 patients treated for mediastinal Hodgkin's disease. In nine of these, the tissue doses had been 2 000 R or less and the treatment period, 3 months or less. VAETH (1962) investigated 45 cases of recurrent mediastinal Hodgkin's disease and suggested a target dose of 3 500 R but gave no treatment period. FULLER et coll. (1967) recommended 3 500 to 4 000 rad over 4 weeks.

Table 1

Dose/time data recommended for treatment in Hodgkin's disease

Author (s)	Dose/time data
Hohl et coll. (1951)	3 000—4 000 rad/?
Nice & Stenstrom (1954, 1955)	2 000 tissue roentgens/3 weeks
Healy et coll. (1955)	1 500—2 500—4 000 R/1 to 3 weeks
Jelliffe & Thomson (1955)	3 500 R/3.5 to 4 weeks
Elkins (1956)	3 000—3 500 R/2 weeks
Peters & Middlemiss (1958)	2 500—3 000 R/2 weeks
Levitt (1959)	2 500 R/2 weeks
Vaeth (1962)	3 500 R/?
Arthachinta & Ogden (1962)	2 000—2 800 roentgens/2 to 3 weeks
Crosbie (1962)	3 500—4 000 R/3 to 6 weeks
Kaplan (1962, 1966)	3 500—4 000 rad/3 to 4 weeks
Easson & Russel (1963)	2 500—2 750 rad/3 weeks
Salzman et coll. (1964)	2 400—3 500 R/3 weeks
Aisenberg (1964)	3 500 R/3.5 to 4 weeks
Jelliffe (1965)	2 500—4 000 rad/2 to 4 weeks
Newall (1965)	2 000—2 500 rad/2 weeks
Easson (1966)	3 000—3 250 rad/3 weeks
Fuller (1967)	4 000 rad/4 weeks
Fuller et coll. (1967)	3 500—4 000 rad/4 weeks
Friedman et coll. (1967)	3 500 rad/4 weeks
Seydel et coll. (1967)	3 500—4 000 rad/4 weeks

The total treatment time (Strandqvist 1944) as well as the total number of fractions (Ellis 1963) in fractionated radiotherapy are important. Most studies on split-course radiotherapy have been made on human cancers or animal tumours. Scanlon (1963), however, in a casuistic report of split-course radiotherapy for mediastinal Hodgkin's disease reported good regression of the lymphomas in the interval between the two series after 1 350 R. Holsti (1966) found that the end results of split-course radiotherapy of human cancers were not inferior to those after continuous irradiation, though doses administered in the former cases were larger. Holsti had often noted shrinkage of the tumours during the interval between the two series. Sambrook (1963) claimed that treatment must be resumed before recovery of the mitotic activity in the tumour but added that this interval is unknown, although he had never seen clinical evidence of renewed growth in human epitheliomas within the first 6 to 8 weeks after 2 000 to 2 500 R given over 2 to 3 weeks. Du Sault (1954), in a study using different fractionation types of irradiation of spontaneous mammary carcinoma in mice, reported that continuous treatment produces better results than split-

Table 2

Comparison of patients without and patients with clinically diagnosed recurrences in relation to sex, age, clinical stage, histologic type and fractionation — Median values and ranges are given for age and fractionation data

	Group A = Mediastinal recurrence not diagnosed clinically	Group B = Mediastinal recurrence diagnosed clinically
Males: females	6: 5	5: 3
Age (years) at first mediastinal treatment	31 (15—48)	27 (16—45)
Clinical stage at first mediastinal treatment: I	1	0
Clinical stage at first mediastinal treatment: II	8	7
Clinical stage at first mediastinal treatment: III	2	1
Histologic type in biopsy specimen:		
Lymphocytic predominance	3	1
Nodular sclerosis	4	5
Mixed cellularity	4	2
Lymphocytic depletion	0	0
Treatment period (days):		
First series	22 (11—32)	25 (17—32)
Second series	13 (6—17)	12 (8—54)
Totally	71 (56—89)	76 (61—131)
Number of fractions:		
First series	20 (12—24)	21 (16—24)
Second series	12 (6—16)	8 (8—16)
Totally	32 (19—36)	32 (24—33)
Interval (days) between the series	38 (31—49)	41 (31—47)

course therapy. The later the interval in split-course treatment the better were the results. Though no direct correlation could be shown, the end-results tended not to be as good when the interval was long as when it was short. SCANLON (1960) stated that the recovery time for tumours varies from patient to patient. FRIEDMAN et coll. (1967) produced an isoffect recovery curve indicating that Hodgkin's disease was capable of recovering from the effects of radiation. This recovery resembled that of carcinoma more closely than that of a radiosensitive lymphoma, such as *mycosis fungoides.*

The aim of the present retrospective investigation was to find out whether any difference in the target dose level was demonstrable between patients without and patients with clinically diagnosed recurrences after initial radiation treatment for mediastinal Hodgkin's disease. It was decided to study the lymph node group in the mediastinum (1) because this region is often involved early in

progressive disease (LANDBERG & LARSSON 1968, 1969), (2) because the geometrics for mediastinal irradiation is fairly well defined, and (3) because the results of therapy may be verified by roentgen examination.

Material and Follow-up. A total of 246 patients with Hodgkin's disease were referred to the department during the period 1944—1960, and 149 of these, who were previously untreated, were admitted. Re-examination of the biopsy specimens obtained before the beginning of treatment had invariably verified the diagnosis. The patients had been followed-up by the system described by LINDGREN (1962). The period covered by the present investigation allowed a follow-up of at least 5 years from the commencement of treatment.

The material was divided according to the clinical staging of the disease (JELLIFFE & THOMSON 1955, JELLIFFE 1965):

Stage I. Lymph node involvement in only one main group but not including intra-abdominal disease.

Stage II. Lymph node involvement of 2 or more groups in the upper or lower half of the body but not including intra-abdominal disease.

Stage III. Generalized lymph node involvement — intra-abdominal involvement — involvement of structures other than lymphatics — constitutional symptoms for which no other reasonable cause can be found.

The material was divided according to the histologic type of lesion (LUKES et coll. 1966), as follows: lymphocytic predominance — nodular sclerosis — mixed cellularity — lymphocytic depletion. Further details of the materials are given elsewhere (LANDBERG & LARSSON 1969, LANDBERG 1969).

Fifty-six patients in all received radiation for mediastinal lymphomas (re-irradiation for recurrence excluded). Lymphadenopathia at the site of treatment after the initial course of radiotherapy was regarded as a recurrence (KAPLAN 1966). Of the 56 patients, 29 were excluded from this series: one in whom the treatment had been given in one series only, eighteen mostly with advanced disease who had been followed-up for at the most one year after the treatment of the mediastinum, and ten whose roentgenograms were not available for review. In none of the remaining 27 patients had any mediastinal recurrence been diagnosed clinically within less than 26 months of the first irradiation of the mediastinum. It was therefore decided to exclude a further eight patients who had been followed-up for less than 26 months after the first mediastinal irradiation.

The series thus consisted of 19 patients with mediastinal Hodgkin's disease followed up for 3 years or more after the first treatment of the mediastinum. The examinations had revealed mediastinal recurrence in eight (group B) but not in the remaining eleven (group A) patients.

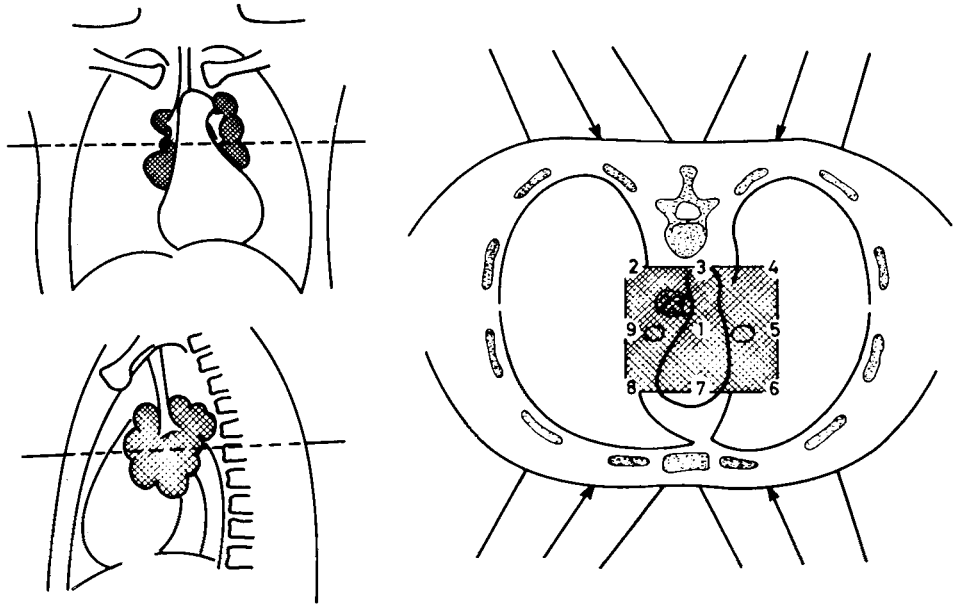

Fig. 1. Example of reconstructed contour and of irradiation geometry in mediastinal Hodgkin's disease.

Radiation data and estimation of the doses given. The treatment in all the nineteen patients had been given as split-course therapy in two series (Table 2). Irradiation had been given in fifteen of the patients with 170 kV roentgen rays (HVL 0.9 mm Cu) and two ventral and two dorsal oblique portals, in one (No. 158) with 170 kV roentgen and two ventral portals, in one (No. 114) with 200 kV roentgen and rotation and in two (Nos 94 and 128) with ^{60}Co and one ventral and two dorsal portals. One field was irradiated daily and the treatment was given 6 days a week.

Information about doses in clinical materials should be founded on individual dose-planning made at the time of treatment. Such precise information is, however, seldom included in clinical reports, and the various ways employed in reporting doses given to patients make it difficult to compare the therapeutic results obtained in different clinics (Ellis 1963).

In the present material, chest roentgenograms taken at the beginning of treatment and later during follow-up were available. Reconstructions were drawn for all the nineteen patients of a contour through the centre of the mediastinal lymphoma by means of the roentgenograms that had been obtained at the beginning of treatment (Fig. 1). The roentgenographic enlargement factor was taken as 1.10 for a.p. views and 1.15 for lateral views. The error in such reconstructions

may be considerable in the lateral parts of the contour but can be kept within reasonable limits in the medial parts. In ten patients, the reconstructed contours were checked either with contours made at the time of treatment or with those obtained at a review. The reconstructed contours in the medial parts in these ten patients agreed well; the difference in a.p. distance was found to be within ± 1 cm. It is apparent from Fig. 1 that only the medial parts of the contours are of interest in the further discussion.

The patient records contained information on the surface absorbed dose, type and energy of radiation, geometric field sizes and angle of incidence. The dose delivered to nine different points (Fig. 1) was calculated with the assumption that the volume treated was comparable to water-equivalent tissue from the point of view of radiation absorption (Clinical Dosimetry, ICRU Report 10d, 1963). The dose to the target volume varied noticeably in the 4-portal technique (Fig. 1). In addition, the lateral parts of the target volume were prone to fall outside the radiation fields, even with slight variation of the angle of incidence, and thus a minor variation in the set-up could result in considerable changes in the distribution of the dose delivered. The patients were, however, young, mostly in good general condition, and presumably cooperated well. Roentgenologically, the regression of mediastinal lymphomas is centripetal and this was noted in sixteen of the nineteen patients by the time the second series was started. When it occurs, the degree of reproducibility of the geometry probably becomes less critical.

The treatments have thus been expressed as the doses to the centres of the target volumes and disregard the dose variation in the peripheral parts of the target volumes.

Dose measurements were made in phantoms in order to estimate the error involved by the assumption that the irradiated tissue was water-equivalent. A volume in a Machlett-Alderson Rando Phantom (Machlett Laboratories, Inc. Springdale, Connecticut, U.S.A.) with skeleton and simulated lung tissue was irradiated with the 4-portal technique (Fig. 1). A phantom of the same dimensions but consisting only of water-equivalent material was then made and a corresponding volume was irradiated. Dose measurements were made with individually calibrated thermoluminiscence dosimeters (lithium borate in teflon). The measured dose delivered to the centre of the target volume in the Alderson phantom was 111 ± 2 rad S.D. (overall uncertainty), based on the maximum absorbed surface dose of 100 rad for a single field. The corresponding figure for the homogeneous, water-equivalent phantom was 106 ± 2 rad S.D. The calculated dose to the centre of the target volume was 100 rad. If it be accepted that this experiment can be used as a guide in the evaluation of the doses calculated for the patients, then a correction of the calculated dose to the centre

of the target volume by reason of heterogeneous tissue should be in the order of + 10 %. We have, however, only indicated the calculated dose in the text. The correction factor for determination of the absolute dose should then be 1.1. A similar figure has been given by JACOBSON & KNAUER (1956), who made measurements with ionization chambers in a phantom man made of presdwood and having a cork lung.

Results and Discussion

Comparison between findings in patients without recurrence and patients with recurrences irrespective of dosage. The second treatment series was prolonged to 54 days in one patient (No. 11-B), but otherwise the patients in group A and in group B were comparable (Table 2) as regards distribution according to sex, age, clinical stage, histologic type and fractionation. The height of the irradiation fields was 10 to 18 cm in the patients in group A and 11 to 22 cm in the patients in group B.

Three of the patients in group A (Nos 47, 74 and 114) and one of the patients in group B (No. 11) had also extra-mediastinal manifestations which had not been treated when the mediastinal irradiation was completed.

Roentgen examination before the beginning of the second series revealed no abnormality in four of the patients in group A (Nos 29, 72, 74 and 94) and in one of the patients in group B (No. 150).

The mediastinal recurrences were diagnosed 26 to 92 months (mean 60) after the irradiation of the mediastinum. Of the eleven patients in group A, eight had been followed-up for 5 years or more, and six for more than 8 years after the beginning of the mediastinal irradiation. In the series of KAPLAN (1966) and of SEYDEL et coll. (1967) recurrences and extensions tended to occur within 2 to 3 years of the beginning of treatment of Hodgkin's disease. In the present series, at first all patients with a follow-up of at the most a year were excluded; among the remainder recurrences were not diagnosed until 26 months or more after irradiation of the mediastinum had been started.

Treatment with cytotoxic drugs had been initiated before the first irradiation of the mediastinum in three of the patients in group A (Nos 85, 114 and 158) but in none of the patients in group B. Later, five more patients in group A and all patients in group B received cytctoxics. Such treatment had been started in five of the eight patients in group B before the mediastinal recurrence had been diagnosed.

Further manifestations of Hodgkin's disease at other sites were diagnosed later in six of the patients in group A at 4 to 68 months (mean 32) and in all the eight patients in group B at 1 to 191 months (mean 42) after the beginning

Table 3

Treatment data for each one of the patients and interval between the first mediastinal irradiation and clinical detection of recurrence in patients with and without mediastinal recurrences — L denotes living patients and D those who died

	Patient No.	Dose to centre of target volume (rad)	Total treatment period (days)	Total number of fractions	Follow-up after first mediastinal irradiation (months)	Mediastinal recurrence after first irradiation (months)
Group A = Mediastinal recurrence not diagnosed clinically	29	4 100	89	32	159 L	
	47	3 600	82	36	122 D	
	58	4 400	89	36	175 L	
	72	3 900	82	36	150 L	
	74	5 500	68	30	43 D	
	85	3 700	71	32	137 L	
	94	5 000	67	30	54 L	
	112	4 200	61	28	104 L	
	114	3 600	60	19	50 L	
	128	4 400	74	33	60 L	
	158	3 400	56	20	60 L	
Group B = Mediastinal recurrence diagnosed clinically	6	3 500	83	33	197 D	92
	11	3 900	131	32	39 D	26
	38	3 400	77	32	83 D	51
	40	3 400	75	30	56 D	51
	50	3 100	80	32	81 D	75
	95	3 000	61	28	95 D	73
	139	3 500	75	32	93 L	73
	150	4 300	66	24	58 D	35

of the mediastinal irradiation. The mediastinal recurrence was the first new sign of Hodgkin's disease after the irradiation of the mediastinum in two of the patients in group B (Nos 6 and 139).

Comparison between patients without and patients with recurrence in relation to dosage. A review of the roentgenograms obtained before completion of the irradiation of the mediastinum revealed changes in the pulmonary parenchyma or pleurae in five of the nineteen patients. The changes were located outside the irradiation fields in three patients (Nos 74, 95 and 150). Such changes, though slight, were seen within the irradiation fields in two patients (Nos 112 and 114).

The data for each one of the patients are assembled in Table 3, giving the calculated dose to the centre of the target volume, the treatment period, the

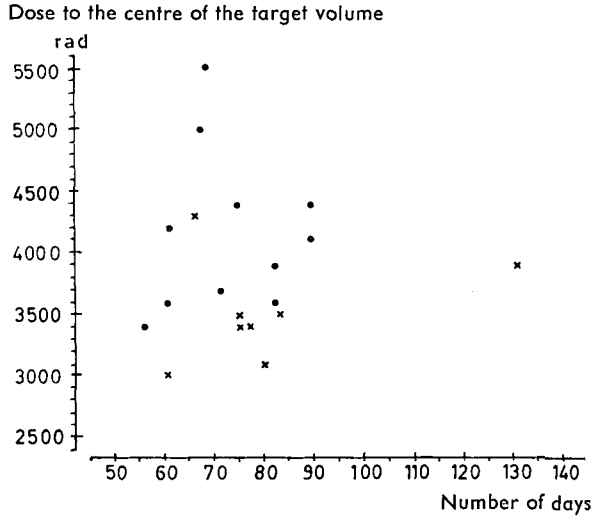

Fig. 2. Dose to the centre of the target volume distributed at different treatment periods (days) for patients without recurrence (●) and for those with clinically diagnosed mediastinal recurrences (×).

number of fractions and the follow-up, and, for the patients in group B, also the recurrence-free interval.

The dose to the centre of the target volume for patients without and with clinically diagnosed recurrences is recorded in Figs 2 and 3, related to the treat-

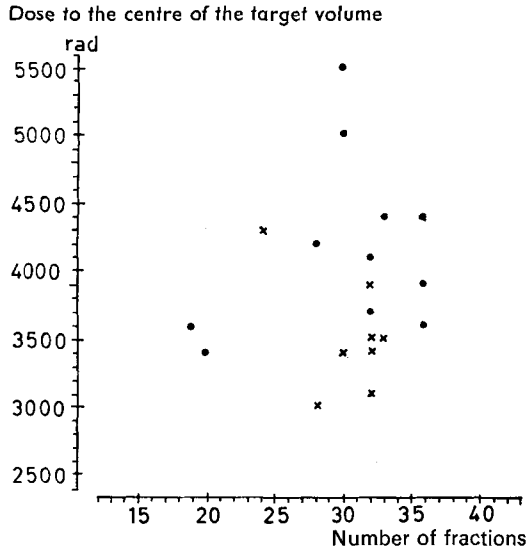

Fig. 3. Dose to the centre of the target volume distributed with different number of fractions for patients without recurrence (●) and for those with clinically diagnosed mediastinal recurrences (×).

ment period (Fig. 2) and to the number of fractions (Fig. 3). It is apparent that for a given number of days, or with a given number of fractions, recurrences were more common among patients who had received smaller doses. For a given dose level, the frequency of recurrences seemed to diminish with a decreasing number of days and a decreasing number of fractions. It was not possible, however, to analyze the material in order to obtain a fractionation curve.

The presence or absence of a recurrence in the present material thus tended to vary with the calculated dose to the centre of the target volume in relation to the treatment period and to the number of fractions, but not with any other of the factors studied. The treatments were administered within (median) 75 days and in (median) 32 fractions, and it seemed that in these intervals, the dose to the centre of the target volume should not be below 3 600 rad if it is to be effective. The dose would be about 4 000 rad with the correction factor of 1.1 for inhomogeneous tissue.

Autopsy was performed in one of the group A patients who had died (No 47); the cause of death was Hodgkin's disease. The examination revealed signs of the disease in a node in the mediastinum.

Acknowledgements

The authors wish to thank I. Bång of the Department of Roentgen Diagnosis for help with the re-evaluation of the roentgenograms. The work was supported by grants from the Swedish Cancer Society.

SUMMARY

Doses delivered to the centres of the target volumes were calculated retrospectively in nineteen patients followed up for at least 3 years after split-course irradiation for mediastinal Hodgkin's disease. There were eleven patients without recurrences who were compared with eight patients in whom recurrences had been diagnosed clinically. The development or absence of a recurrence seems to depend mainly on the size of the dose to the centre of the target volume.

ZUSAMMENFASSUNG

Die zum Zentrum des Bestrahlungsgebietes gelieferten Dosen in neunzehn Patienten mit Hodgkinscher Krankheit des Mediastinums, die für ein Minimum von 3 Jahren nach fraktionierter Tiefenbestrahlung unter Kontrolle gehalten werden konnten, wurden retrospektiv berechnet. Ein Vergleich konnte zwischen elf Patienten, die rezidivfrei waren, und acht Patienten, die klinisch Rezidive hatten, angestellt werden. Das Auftreten von Rezidiven scheint im wesentlichen von der Grösse der Dosis im Zentrum des Bestrahlungsgebietes abhängig zu sein.

RÉSUMÉ

Les auteurs ont calculé rétrospectivement les doses délivrées au centre des volumes cibles chez 19 malades suivis pendant trois ans au moins après irradiation fractionnée pour maladie de Hodgkin médiastinale. Ils ont comparé onze malades sans récidive et huit malades chez lesquels on avait fait le diagnostic clinique de récidive. L'apparition ou l'absence d'une récidive paraît dépendre surtout de la dose calculée au centre du volume cible.

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