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FROM THE DEPARTMENTS OF ONCOLOGY AND RADIATION THERAPY, AND RADIATION PHYSICS, UNIVERSITY HOSPITAL, S-221 85 LUND, SWEDEN.

HODGKIN'S DISEASE IRRADIATED WITH THE INVERTED-Y TECHNIQUE

C. E. MERCKE, I. YABE, T. G. LANDBERG and G. O. SVAHN-TAPPER

Extended-field radiation therapy is being widely used in the treatment of Hodgkin's disease. It was recommended as early as 1931 by GILBERT & BABAÏANTZ, but did not become feasible until the sixties when high voltage radiation units became widely accessible.

The extended-field irradiation is given with the mantle technique or with the inverted-Y technique, depending on stage and site of the disease, often the two techniques or part of them are combined. For each technique, the target volume has to be defined properly, and the target absorbed dose and its fractionation prescribed. The total target absorbed dose to be aimed at is usually considered to be of the order of 40 Gy given with fractions of 10 Gy per week (KAPLAN 1966).

Even though combination chemotherapy often is effective after unsuccessful irradiation, there seems today to be little need for adding chemotherapy to carefully performed extended-field radiation therapy in supradiaphragmatic Hodgkin's disease (DUCHAMP et coll. 1977, HELLMAN et coll. 1978, ROSENBERG et coll. 1978, TIMOTHY et coll. 1978). The advantage is apparent when considering the late effects of combination chemotherapy, such as sterility and second malignancy. Therefore the technical aspects of extended-field radiation therapy must receive careful attention.

Several reports have appeared on recurrence rates and patterns after mantle irradiation of Hodgkin's disease as well as complications, but surprisingly few after irradiation with the inverted-Y technique.

The purpose of the present report is to describe the technique of inverted-Y irradiation in Hodgkin's disease used at this department, the results gained and the side effects encountered.

Material and Methods

The total series consisted of 40 patients with Hodgkin's disease who were irradiated with the inverted Y-technique during the years 1967 to 1976. Six patients did not complete the treatment because of distant progressive disease. The material then consisted of 34 patients, with a male : female ratio of 24 : 10 and an age range of 14 to 65 (median 37) years. The total follow-up ranged between 1 and 11 years with a mean of 4.8.

The staging procedures included history, physical examination, chest radiography, lymphography, bone marrow examination (biopsy or aspiration), scintigraphy and percutaneous fine needle aspiration biopsy of the liver and spleen, and from 1971 staging laparotomy (22 patients). Three patients had lymphocyte predominance, 12 nodular sclerosing type, 17 mixed cellularity and 2 lymphocyte depletion.

Twenty-five of the 34 patients had been treated previously for supradiaphragmatic Hodgkin's dis-

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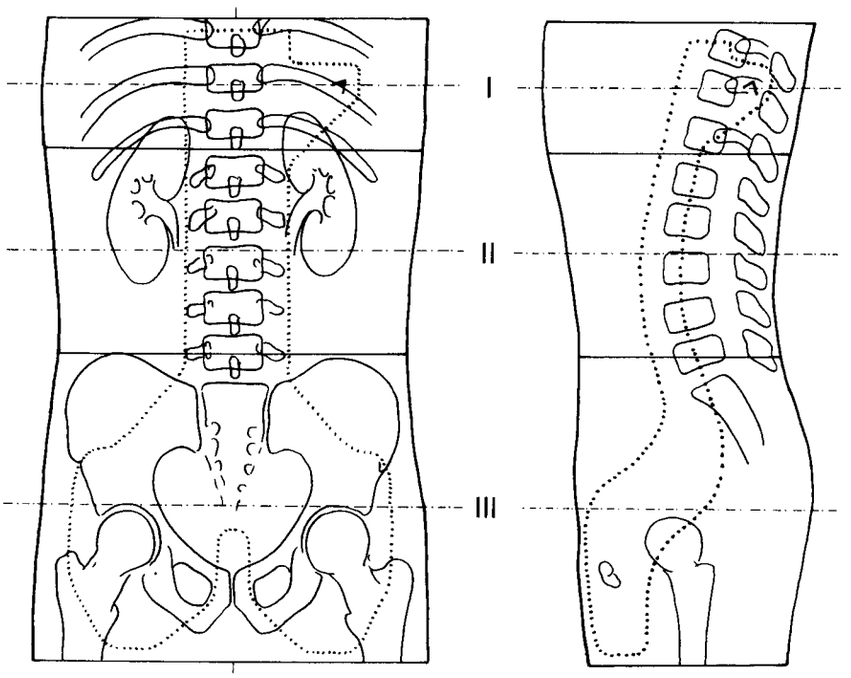

Fig. 1. Target volume in irradiation with the inverted-Y technique of a standard patient without bulky disease. Border of target volume is indicated by the dotted lines. For the dose planning, the patient is, corresponding to the target volume, considered to consist of a stack of 3 slices, each being represented by a section (Nos I, II, III).

ease: the patients in the present series represent infradiaphragmatic location. When staging the patients, any previously treated site was considered. Thus, 4 patients were in stage I, 3 in stage II and 27 in stage III. At the time of treatment with the inverted-Y technique only 2 of the 34 patients had obvious disease above the diaphragm, 8 had systemic symptoms, 7 of them belonged to stage III.

The definition of the target volume agreed with the description of the lymph node topography in standard text books (e.g. FUCHS et coll. 1969). The target volume (Fig. 1) included the lymph nodes along the vertebral column up to the middle of Th10 (=lower border of the target volume in mantle treatment, SVAHN-TAPPER et coll. 1976), the iliac and the inguinal nodes, and the nodes in the obturator foramen and in the oval fossa. In the groin, the lateral nodes were also included. In splenectomized patients the splenic pedicle, as indicated by a metallic clip, was included, and this part of the target volume extended from the position of the clip downward towards the first lumbar vertebra. If pathologic findings had been made during the staging procedures, then the affected tissues were included with a margin of at least 1 cm. In cases where the target volume had been defined according to lymphography, at least a 1 cm margin was also used. If lymphography had been unsuccessful, the extreme lateral border of the transversal processes of the vertebral bodies was taken as the lateral border of the target volume in the a.p. projection.

The organs at risk are the spinal cord, the kidneys, the gastrointestinal tract including the liver, the bone marrow and the gonads.

The irradiation was planned individually for each patient, and for the purpose of planning the patient was considered to consist, corresponding to the target volume, of a stack of three slices (Fig. 1), each being represented by a section. The anatomic details were obtained from 2 orthogonal radiographic films of known magnification. A complete dose plan was made for each section, and included correction for tissue heterogeneity (vertebral bodies). The patients were treated in the supine position only. They were immobilized either in whole-body casts (LANDBERG et coll. 1977) or only at the feet. Typical distribution of absorbed dose appears i Fig. 2.

The irradiation was given with either 8 MV roentgen rays (linear accelerator) or ^{60}Co gamma rays. The fields were positioned on the patient under fluoroscopy using a simulator. During the whole treatment period, repeat films were obtained to control

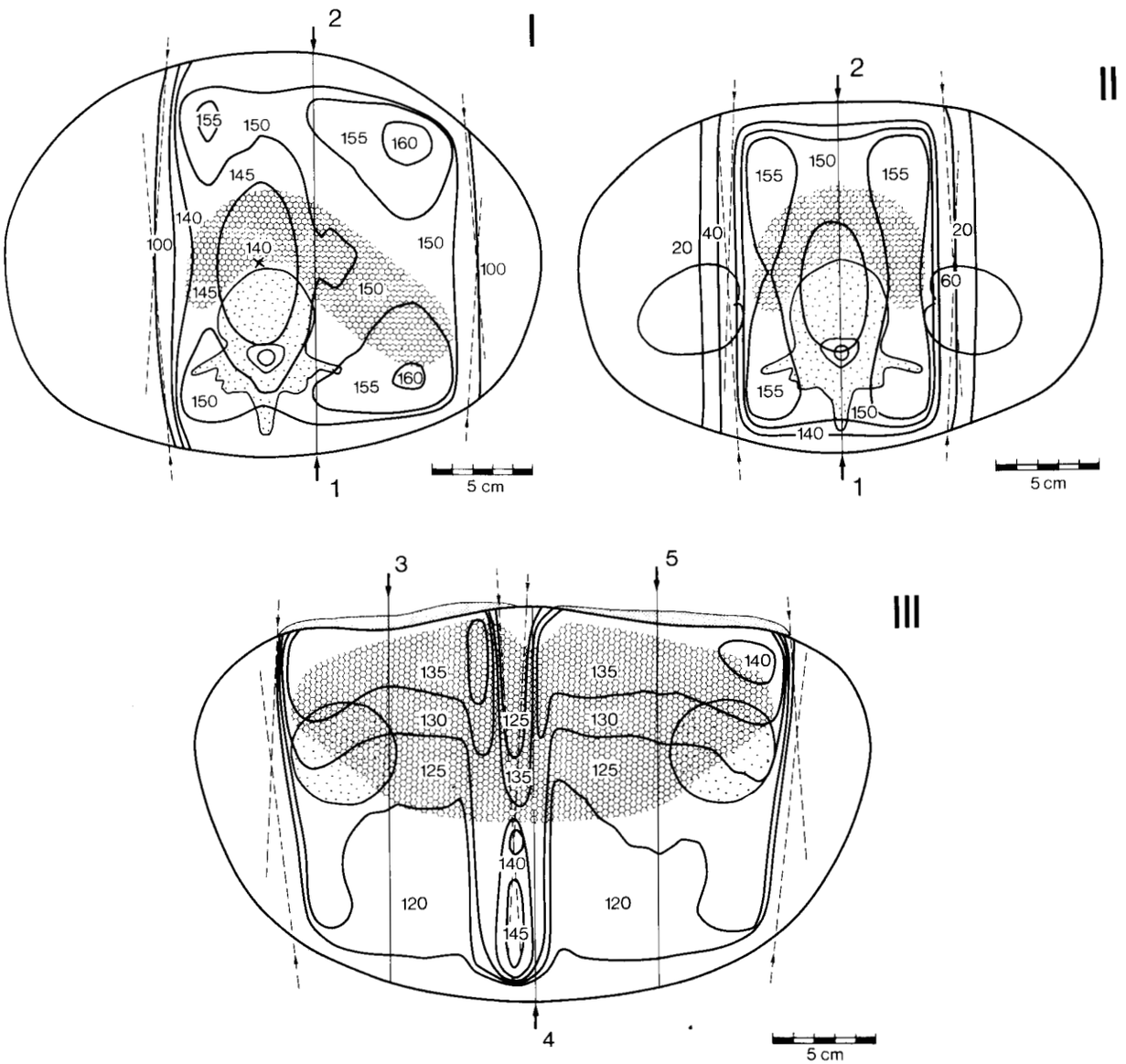

Fig. 2. Dose plans for each of the 3 sections (from MÖLLER et coll. 1976). 8 MV. 100 cm SSD. No wedge filter. Section I—Fields 1 and 2: 100%. 15 cm×20 cm. Section II—Fields 1 and 2: 100%. 10 cm×20 cm. Section III—Field 3: 100%. 11 cm×23 cm. Field 4: 80%. 23 cm×21 cm. Field 5: 100%. 13 cm×23 cm.

the geometry of the set up. The control measures further included measurements of absorbed dose at the beam entrance and exit, and at the gonads (at the scrotal skin or in the rectum dorsally of the operatively transposed ovaries, respectively). Furthermore, the patient's weight was controlled regularly. When irradiating males, the caudal ventral beam was divided into two (Fig. 1), allowing the gonads to be pulled away from the beam; for the dorsal caudal beam, the testes were shielded by a 6.5 cm thick lead block in the midline and the testes were pulled downwards. When treating females, the transposed ovaries were shielded by a 6.5 cm thick tungsten block placed centrally together with a 4 cm lead block near the patient.

The total target absorbed dose was 40 Gy specified as minimum target absorbed dose (ICRU Report 29, 1978). For the upper part of the target volume (sections I and II, Figs 1, 2) this usually equalled the central absorbed dose, because of correction for

tissue heterogeneity. For the caudal section (No. III), it usually corresponded to the absorbed dose most dorsally in the target volume (125% in Fig. 2).

All fields were irradiated at each fraction, 5 fractions being given each week. All patients except one were irradiated according to a split-course schedule with two thirds of the total target absorbed dose in the first series and the remaining third after an interval of 3 to 4 weeks. The target absorbed dose at each fraction was 1.75 Gy, which means that usually 25 Gy were given in the first series in 14 fractions over 20 days and 15 Gy in the second series in 9 fractions over 12 days. The total irradiation period then amounted to 8 to 10 weeks. The CRE-value for this type of split-course treatment is of the order of 11 or 12, depending on whether gap correction is performed according to WINSTON et coll. (1969) or KIRK et coll. (1975). For the patient who was given the total dose in one series only the CRE-value for the specified target absorbed dose was 12.9.

After the treatment period the patients were evaluated every 3rd to 6th month by physical examination, routine hematologic tests, liver and kidney function tests, chest films and abdominal conventional films, and lymphography when indicated. Symptoms of side effects were asked for, e.g. Lhermitte's sign, diarrhea, constipation or abdominal cramps. The blood pressure was measured.

The definitions of response and relapse agreed with the recommendations laid down by KAPLAN (1966) and HAYWARD et coll. (1977).

Chemotherapy was not given as an elective measure, and only when the patients relapsed after the irradiation. Then, combination chemotherapy (MOPP=mustine, vincristine, procarbazine and prednisolone) was usually used.

Survival was calculated from the first day of irradiation.

Results

Survival

The irradiation with the inverted-Y technique was completed in 34 of the 40 patients. Twenty-six are alive with no evidence of disease, 17 after the inverted-Y irradiation only and 9 after further treatment for relapse (Table). Survival, and survival with no evidence of disease, 1 to 10 years after beginning of the irradiation are given in Figs 3 and 4 for patients without and with systemic symptoms. Survival was significantly better for patients without systemic

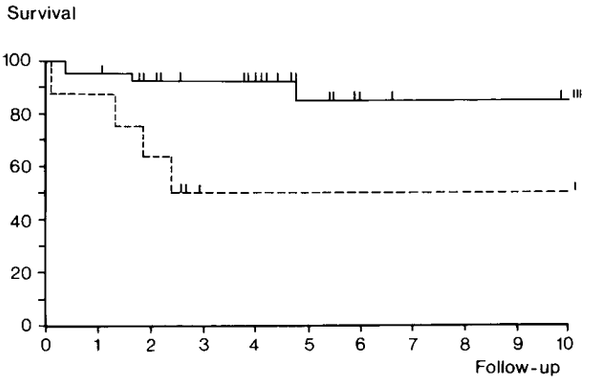

Fig. 3. Survival in per cent (Kaplan-Meier) after irradiation with the inverted-Y technique. Twenty-six patients without systemic symptoms (——), 8 patients with systemic symptoms (- - -). $p<0.05$ (log rank test).

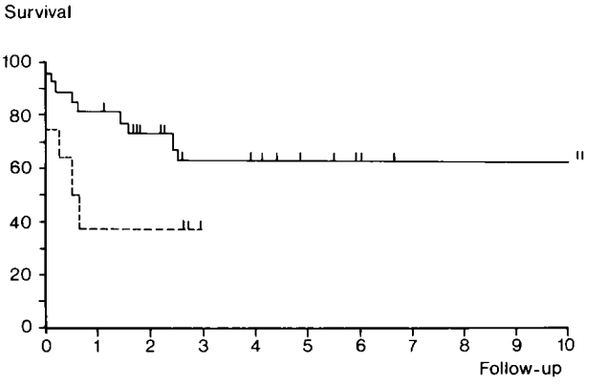

Fig. 4. Survival without evidence of disease in per cent (Kaplan-Meier) after irradiation with the inverted-Y technique. Twenty-six patients without systemic symptoms (——), 8 patients with systemic symptoms (- - -). Five patients did not achieve a complete remission. $p=0.18$ (log rank test).

symptoms. Of the 17 patients alive with no evidence of disease after treatment with the inverted-Y technique only, 11 were males and 6 females. Their ages ranged between 14 and 59 years with a mean of 37. Three had lymphocyte predominance, 7 nodular sclerosing type and 7 mixed cellularity. Four patients belonged to stage I, one to stage II and 12 to stage III. One of the patients stage III had systemic symptoms, but has not relapsed 3 years after irradiation. It may be noted that all patients stage I and II in the total series have remained alive with no evidence of disease after irradiation with the inverted-Y technique with or without further therapy.

Of the 9 patients who are alive without evidence of disease after later treatment for relapse, 7 had a complete remission after irradiation with the inverted-Y technique. Relapse was diagnosed 3 months to

Table

Results in 34 patients who completed irradiation with the inverted-Y technique

	Stages I or II (n=7)	Stage III A (n=20)	Stage III B (n=7)	Total (n=34)
Alive without evidence of disease after inverted-Y irradiation	5	11	1	17
Alive without evidence of disease after further treatment	2	6	1	9
Died	–	3	5	8

6 years (mean 22 months) later, no true or marginal recurrence occurred in this group. One patient belonged to stage I, one to stage II and 7 to stage III. Two had systemic symptoms, 3 had nodular sclerosing type and 6 mixed cellularity. Further therapy was irradiation alone for 2 patients, chemotherapy alone for 4 and combined irradiation and chemotherapy for 3.

All 8 patients who died were males between 19 and 65 years (mean 43). All were in stage III and 5 had systemic symptoms. One had nodular sclerosing type, 6 mixed cellularity, and one lymphocyte depletion. Five of the 8 patients had a complete remission after irradiation with the inverted-Y technique, but all of them died later in progressive disease 3 to 58 (mean 20) months after irradiation. In one of them, the fatal outcome may be attributable to radiation side effects. This patient had a wide-spread disease and was the one who was given one series only. He developed gastrointestinal ulcerations.

Failure

Of all 34 patients given the total dose 29 had a complete remission; of the 5 patients who did not respond primarily 2 could be cured, but 3 died.

Recurrence. Only one of the patients may be assumed to have had a recurrence (true or marginal). He died 6 months after treatment, and postmortem examination revealed dissemination of the disease in the groins, spleen, liver, and bronchopulmonary nodes. The patient had the lymphocyte depletion type of the disease.

Progressive disease occurred in 12 cases. They were diagnosed 6 to 33 months (mean 17.6) after irradiation with the inverted-Y technique, earlier for those who died later (8.8 months) than for those who were cured (18 months; $p<0.01$). Additional lymph nodes were affected in 8 cases (in the neck or submaxillary region in 4 patients, in the supraclavicular region in 2, in the mediastinum in one and in the axilla in one), and in one case the soft tissues of the chest wall were infiltrated; appearance of systemic symptoms indicated failure in 3 patients.

Influence of systemic symptoms. Three of the 29 patients with complete remission had systemic symptoms. One of them remained symptom-free after irradiation, whereas 2 relapsed, both being cured by further treatment.

Side effects

Renal. Before treatment one patient had hypertension, defined as an increase in either systolic blood pressure over 160 or diastolic over 100 mm Hg. The hypertension remained unchanged during follow-up. None of the other patients had hypertension at follow-up. Renal function as evaluated by determinations of serum creatinine was unchanged both in the treatment period and afterwards.

Hepatic. The liver function was followed by means of serum levels of bilirubin, alkaline phosphatase, aminotransferases, and γ-glutamyltransferases, all being unchanged at follow-up.

Gastrointestinal reactions during the irradiation period did not necessitate changes in the fractionation. Slight symptoms of nausea and diarrhea occurred in all patients. However, one patient died 20 months after completed treatment. Postmortem examination revealed disseminated organ infiltration but also multiple non-malignant erosions in the gastric and intestinal mucosa. This patient was the one who had been given the total dose in one series only. The erosions had caused bleeding, and might have contributed to the fatal outcome. None of the 26 patients alive without evidence of disease have symptoms attributable to gastrointestinal radiation side effects.

Hematologic. Usually only a slight decrease in white cell and platelet counts occurred during the ir-

radiation. However, in 2 patients the decrease was so large that the irradiation had to be discontinued for 5 and 7 days, respectively. These 2 patients also had a protracted pancytopenia, which lasted for 2 years in one of them and for 18 months in the other with isolated thrombocytopenia for another 6 months. A third patient had thrombocytopenia after the irradiation series lasting for 4.5 years. None of these 3 patients had any symptoms related to this temporary marrow dysfunction, and no attempts were made to correct it.

Spinal cord. No symptoms or signs of radiation cord reactions occurred.

Gonads. In vivo dose measurements indicated that the absorbed dose at the testes had been of the order of 4 Gy and at the ovaries of the order of 4 to 10 Gy. None of the patients have, to our knowledge, had any children after the treatment, but it should be recalled that the median age in the patient series was rather high (37 years).

Discussion

Since 1971, radiation therapy of infradiaphragmatic Hodgkin's disease stage I, II, or III has been given in this department with the inverted-Y technique. Hodgkin's disease stage I or II occurs only infrequently below the diaphragm (KRIKORIAN et coll. 1979). In the present series, 7 patients had stage I or II. Of the remaining 27 patients who completed the treatment and belonged to stage III (also including in the staging any lesions previously treated), only 2 had not been treated before. Twenty-five of the 27 had previously been irradiated for supradiaphragmatic disease, 15 of them with techniques using fields covering involved regions only and 12 with the mantle technique. At this department, a local relapse rate of only 3 per cent has been obtained with mantle irradiation (SVAHN-TAPPER et coll.). At the time of irradiation with the inverted-Y technique 2 of the 34 patients had disease outside the defined target volume (supradiaphragmatic lymph nodes that were irradiated concomitantly).

Five of the 7 patients stage I or II remained alive without evidence of disease after irradiation with the inverted-Y technique, and the remaining 2 also had a complete remission, but later relapsed. Both were cured by further treatment. One of these 2 patients had systemic symptoms. Thus, the survival rate in stages I or II was 100 per cent, which agrees with recent results in a large Stanford series (ROSENBERG & KAPLAN 1975).

Of the patients in stage III 7 had systemic symptoms. It has been demonstrated that radiation therapy alone does not yield satisfactory results in stage III B disease (JOHNSON et coll. 1970 a, b, GOODMAN et coll. 1977). Of all 8 deceased patients, 5 belonged to stage III B at the time of inverted-Y irradiation, and the results in the present series thus lend support to the opinion that radiation therapy alone is inadequate for stage III B. Adjuvant combination chemotherapy after extended-field irradiation has been reported to prolong the disease-free survival, but overall survival still seems to be the same (ROSENBERG & KAPLAN). However, some other series indicate that adjuvant treatment with combination chemotherapy may be less successful (RUBIN et coll. 1974).

The results of irradiation alone of patients stage III without systemic symptoms are somewhat conflicting in the literature. MILL et coll. (1977) reported a failure rate of 43 per cent, and WELLER et coll. (1976) 30 per cent. Recently STEIN et coll. (1978, 1979) pointed out that anatomic substaging of stage III A had both prognostic significance and therapeutic implications. In patients with upper abdominal involvement (spleen, splenic node, portal node) disease-free survival rate after 5 years was higher for a group of patients given both irradiation and chemotherapy than for patients given irradiation alone, but for both groups the actuarial survival at 5 years was the same because of the effective adjuvant treatment. For patients with lower abdominal disease, however, also a significantly different survival at 5 years was found.

In the present series 20 patients belonged to stage III A. Ten patients had upper and 10 lower disease according to the criteria of STEIN et coll. (1978). In the former group, 8 patients are alive without evidence of disease after treatment with the inverted-Y technique only, and 2 have been cured after treatment for relapse. In the latter group, on the other hand, 3 patients have died, 4 are alive after treatment for relapse, and 3 have remained symptom-free. Actuarial survival for the upper abdominal disease group was 100 per cent and for the lower abdominal group 70 per cent, but the material does not warrant a statistical evaluation.

The only recurrence in the present series was located in distal inguinal nodes and may be labelled as a marginal one. The absence of true recurrences

within the target volume after treatment with the inverted-Y technique may reflect the fact that the target volume was defined rather generously. Furthermore, attention was paid to patient fixation and controls of beam geometry and absorbed dose during treatment. The importance of a precise treatment technique has been emphasized by JOHNSON et coll. (1970 a, b) and by MARKS et coll. (1976). The dosimetry of the inverted-Y technique has been reported on by only a few authors. PAGE et coll. (1970) gave a detailed description of the dose distribution from a 6 MV linear accelerator. They emphasized the risk of giving a high dose to the gonads. They treated patients in both supine and prone positions, and did not report on correction for tissue heterogeneity but included a description on measurements of absorbed dose in an anatomic phantom. GRAY & PROSNITZ (1975) reported on the dosimetry of the inverted-Y technique using a 4 MV linear accelerator. They also emphasized that careful positioning of the testes inferior to the lower border of the field is the main factor to reduce the gonadal dose.

All but one of the patients in the present series were irradiated according to a split-course schedule up to a specified target absorbed dose of 40 Gy. This type of fractionation has proven useful in the irradiation of the upper mantle (SVAHN-TAPPER et coll.) and was also recommended by JOHNSON et coll. (1976). It gives the same cure rate as irradiation in one series only, but may be expected to give less severe radiation side effects. Furthermore, in order to minimize the side effects, all fields should be irradiated at each fraction (MARKS et coll. 1973).

The results of inverted-Y irradiation of Hodgkin's disease are often not so readily correlated with the technique as those after mantle irradiation, since the inverted-Y technique is often used in more advanced stages and then often in combination with chemotherapy. Furthermore, the target volume in the inverted-Y technique does not lend itself to such easy evaluation as that in the mantle technique. Therefore, it is relatively difficult to estimate from the literature the local effectiveness of the inverted-Y technique. Of the 12 cases with progression in the present series, 7 could be attributed to a previous 'old-fashioned' irradiation of supradiaphragmatic disease using fields covering involved regions only. These patients relapsed in remaining untreated supradiaphragmatic lymph nodes after completion of the inverted-Y irradiation.

The side effects in the present series were almost negligible. Only the one patient given one series only developed a serious complication, namely ulcerations of the gastrointestinal mucosa despite the absorbed dose in the mucosa being at the lower border of the range for gastric complications after irradiation given by KELLUM et coll. (1977). Hepatic and renal complications did not occur, and were not anticipated because only relatively small parts of the organs at risk were included in the irradiated volume (ICRU Report 29, 1978). Radiation myelitis was not encountered, and was not anticipated either, since all fields were irradiated at each fraction and the total absorbed dose to the spinal cord was at most of the order of 46 Gy, and often less. It has recently been stated that cord tolerance to well fractionated irradiation is in excess of what has usually been considered (LAMBERT 1978). During the radiation therapy all patients had a slight decrease in white blood cell and platelet counts. Also the hemoglobin concentration was somewhat reduced. The 2 patients in whom the radiation schedule was affected by a depression of blood values were 46 and 53 years of age, respectively, i.e. somewhat older than the mean age of the whole series. The third patient who developed thrombocytopenia after having completed the inverted-Y irradiation was on the other hand younger, being only 31 years. It is interesting to note that all these 3 patients with slight hematologic complications have remained relapse-free after irradiation with the inverted-Y technique only. It has been pointed out that the potential of the bone marrow to repopulate from injury secondary to ionizing radiation is determined by the absorbed dose, age of the patient, and total amount of marrow irradiated. In patients given total nodal irradiation (TNI), RUBIN et coll. (1973) and KNOSPE et coll. (1976) observed regeneration after 40 Gy within 24 months. SACKS et coll. (1978) have presented data on TNI-treated patients supporting these findings, but they also found that regeneration was less when major portions of central marrow were not irradiated. No patient in their series regenerated at absorbed doses above 40 Gy when any major segment of central marrow was not irradiated, and only minimal regeneration occurred at doses around 30 Gy. These authors hypothesized that the destruction of only small parts of the bone marrow, considered as a whole organ, does not serve as an adequate stimulus for regeneration. However, when patients receive TNI a definite dose effect is observed, and areas receiving more than 40 Gy regenerate badly. In the

present series the normal peripheral blood counts after less than 6 months might support the hypothesis that although only part of the marrow was irradiated and thus the stimulus to the regeneration was insufficient, the effect of the absorbed dose of 40 Gy was less, given in a non-split course schedule. This was not the fact in the series of SACKS et coll.

SUMMARY

Thirty-four patients with Hodgkin's disease were treated with the inverted-Y technique. Target absorbed dose was 40 Gy given in a split-course schedule to all but one patient. Only one recurrence occurred. Seventeen patients remained symptom-free after treatment and another 9 were rescued by further therapy. Eight patients died. All 7 patients in stages I and II are alive. In stage III A more patients with upper abdominal disease remained symptom-free after treatment than patients with lower abdominal disease. Of 7 patients in stage III B, 5 died. Actuarial survival at 10 years was significantly better for patients without systemic symptoms. Radiation side effects were mild. One serious complication occurred, acute gastrointestinal ulceration in the patient given the total dose in one series. No permanent symptom-producing side effects from liver, kidneys, spinal cord or bone marrow occurred.

Request for reprints: Dr Claes E. Mercke, Department of Oncology, University Hospital, S-221 85 Lund, Sweden.

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