# Optimal Planning Target Volume for Stage I Testicular Seminoma: A Medical Research Council Randomized Trial

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***Purpose:*** **To compare relapse rates and toxicity associated with para-aortic (PA) strip or PA and ipsilateral iliac lymph node irradiation (dogleg [DL] field) (30 Gy/15 fractions/3 weeks) for stage I testicular seminoma.**

***Patients and Methods:*** **Between July 1989 and May 1993, 478 men with testicular seminoma stage I (T1 to T3; no ipsilateral inguinoscrotal operation before orchiectomy) were randomized (PA, 236 patients; DL, 242 patients).**

***Results:*** **Median follow-up time is 4.5 years. Eighteen relapses, nine in each treatment group, have occurred 4 to 35 months after radiotherapy; among these, four were pelvic relapses, all occurring after PA radiotherapy. However, the 95% confidence interval (CI) for the difference in pelvic relapse rates excludes differences of more than 4%. The 3-year relapse-free survival was 96% (95% CI, 94% to 99%) after PA radiotherapy and 96.6% (95% CI, 94% to 99%) after DL (difference, 0.6%; 95% confidence limits, −3.4%, +4.6%). One patient (PA field) has died from seminoma. Survival at 3 years was 99.3% for PA and 100% for DL radiotherapy. Acute toxicity (nausea, vomiting, leukopenia) was less frequent and less pronounced in patients in the PA arm. Within the first 18 months of follow-up, the sperm counts were significantly higher after PA than after DL irradiation.**

***Conclusion:*** **In patients with testicular seminoma stage I (T1 to T3) and with undisturbed lymphatic drainage, adjuvant radiotherapy confined to the PA lymph nodes is associated with reduced hematologic, gastrointestinal, and gonadal toxicity, but with a higher risk of pelvic recurrence, compared with DL radiotherapy. The recurrence rate is low with either treatment. PA radiotherapy is recommended as standard treatment in these patients.**

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IN PATIENTS WITH stage I testicular seminoma, irradiation of the para-aortic (PA) and ipsilateral iliac lymph nodes (dogleg [DL] field) has been the standard adjuvant treatment for many years, resulting in a 98% to 99% cancer-specific 5-year survival.[1-7] This target volume includes the regional lymph nodes of the diseased testicle in which microscopic tumor involvement is suspected. The rate of severe radiation-induced long-term toxicity is less than 2%.[8] Careful monitoring proves that DL radiotherapy for stage I seminoma leads to clinically significant, although moderately acute, gastrointestinal toxicity in about 60% of the patients[9] and is followed by moderate chronic gastrointestinal side effects in 5%.[8] Furthermore, the risk of a second non–germ cell malignancy within the target volume should not be overlooked. With long-term follow-up, several authors have demonstrated a significantly increased risk of second cancer, particularly in the upper gastrointestinal tract, and of bladder cancer.[10-12] An increased risk of leukemia has also been suggested[13] to be a consequence of irradiation of the pelvic bone marrow. Clinicians would thus welcome successful attempts to reduce the target volume, recognizing that a wait-and-see (surveillance) policy is resource-demanding and not always feasible in the routine clinical management of patients with stage I seminoma.

Increased recognition of the routine testicular lymph drainage (predominantly the PA region), together with patterns-of-failure analyses of surveillance studies,[14-18] has led to the suggestion that microscopic iliac lymph node metastases are extremely rare in stage I seminoma patients with undisturbed testicular lymphatics (no prior scrotal or inguinal surgery). This again suggests that irradiation of the iliac lymph nodes can probably be omitted safely in the majority of these patients, restricting adjuvant radiotherapy to the PA lymph nodes. These studies also demonstrate the fact that only around 15% of patients will relapse without radiotherapy, further emphasizing the need to minimize the morbidity of treatment without compromising efficacy.

With this background, in 1989, the Medical Research Council (MRC) Testicular Cancer Working Party activated a randomized trial (TE10) with the aim of comparing the relapse pattern, survival, and 2-year (that is, early) toxicity

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in stage I seminoma patients irradiated by DL field and those treated with a field comprising only the PA lymph nodes (PA field).

## PATIENTS AND METHODS

### *Eligibility*

Eligible patients had to fulfill the following criteria: (1) histologically confirmed pure seminoma of the testis, including both anaplastic and classic seminoma; (2) stage I disease, according to the Royal Marsden classification system[19] (no demonstrated metastases and normal postoperative serum levels of alpha-fetoprotein [AFP] and human chorionic gonadotropin); an elevated serum AFP level, but not an elevated human chorionic gonadotropin level, before orchiectomy would render a patient ineligible; (3) normal abdominal lymphogram with intravenous urogram, or normal abdominal and pelvic computed tomographic (CT) scans; (4) primary tumor: T1 to T3[20]; (5) no previous ipsilateral inguinal or scrotal operations; (6) interval of 8 weeks or less between orchiectomy and randomization; and (7) patient informed consent.

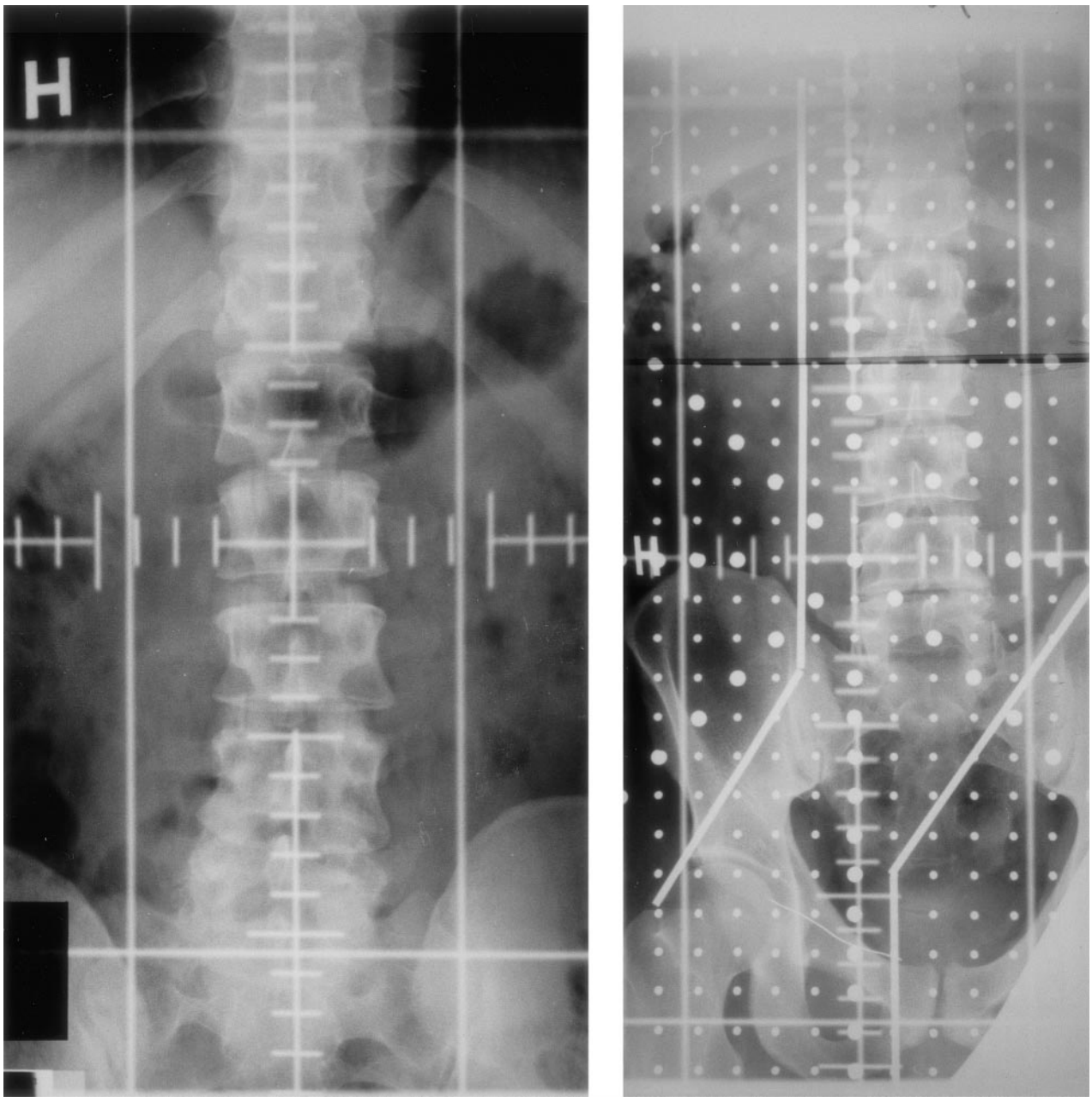


Fig 1. Testicular seminoma stage I. DL and PA fields.

### *Radiotherapy*

All patients were intended to receive a midplane dose of 30 Gy in 15 fractions over 3 weeks given to opposing anterior and posterior fields. Each field was treated daily. The margins of the DL field were as follows: upper border, disk between Th10 and Th11; lower border, mid obturator foramen; ipsilateral margin, to the renal hilum down as far as the disk between the fifth lumbar and first sacral vertebrae (L5-S1), then diagonally to the lateral edge of the acetabulum, then vertically downward to the mid obturator level (Fig 1); contralateral margin, inclusion of the processus transversus in the PA area down to L5-S1, then diagonally in parallel with the ipsilateral border, then vertically to the median border of the obturator foramen.

The PA field was identical to the upper part of the DL field (above the level of L5-S1). Testicular shielding, based on the individual institution's technique, was recommended for patients treated with the DL field who wished to preserve their fertility. The use of antiemetics was left to the clinician's discretion (prophylactic antiemetics were allowed), but in those patients experiencing symptoms, the recommended treatment was prochlorperazine 5 mg orally or metoclopramide 10 mg orally before each fraction. In each patient, the target fields were checked by verification port films, in particular, checking for the inclusion of the ipsilateral renal hilum. Individual measurements of the testicular dose were optional.

### *Follow-Up*

All patients were seen every 3 months during the first year, every 4 months during the second year, every 6 months during the third year, and annually thereafter. At each visit, a clinical examination and a chest x-ray were performed and blood was taken for a serum tumor marker assay. Routine abdominal and pelvic CT scans were to be performed annually during the first 3 years. The simultaneous use of routine chest CT was optional.

### *Assessment of Toxicity*

During the period of radiotherapy, the patient was seen by the responsible radiotherapist at least once weekly. Acute gastrointestinal side effects and hematologic toxicities were assessed weekly. During subsequent posttreatment follow-up visits, clinicians paid particular attention to the development of symptoms of peptic ulceration, and gastroscopy was to be performed routinely in cases of persisting dyspeptic distress. Sperm analysis was to be performed, where possible, before and at 6, 12, and 24 months after radiotherapy.

### *Sample Size*

The trial was designed as an equivalence study in which clinical equivalence would be determined by balancing potential gains from PA irradiation, which would benefit all patients, to potential losses in some patients (specifically, increased pelvic relapse rate, compared with the DL group). The potential benefits included the simpler field set-up, which reduced treatment planning time, and a reduction in acute and long-term toxicity associated with PA strip irradiation. In view of the success of salvage treatment, it was considered that a modest absolute increase in the pelvic relapse rate might be acceptable. The trial was therefore designed to exclude, with 90% power at a 5% significance level, an increase in the 3-year pelvic relapse rates of approximately 3%, assuming a pelvic relapse rate of 1% in the DL field group. This required 400 patients to be randomized.[21]

**Table 1. Patient Demographics**

| Characteristic | Treatment Field: PA Strip No. | PA Strip % | DL No. | DL % |
|---|---|---|---|---|
| No. of patients | 236 | | 242 | |
| Age, years | | | | |
| Median | 36 | | 37 | |
| Range | 21-69 | | 18-71 | |
| Prior bowel operations | | | | |
| No | 226 | | 23 | |
| Yes | 6 | | 8 | |
| Unknown | 4 | | 4 | |
| Prior peptic ulceration | | | | |
| No | 228 | | 234 | |
| Yes | 4 | | 3 | |
| Unknown | 4 | | 5 | |
| WHO performance status | | | | |
| 0 | 221 | | 226 | |
| 1 | 11 | | 13 | |
| Not recorded | 4 | | 3 | |
| Side | | | | |
| Left | 106 | | 101 | |
| Right | 122 | | 134 | |
| Not recorded | 8 | | 7 | |
| Preorchiectomy HCG (U/L) | | | | |
| $\leq 10$ | 164 | | 153 | |
| $> 10$ | 29 | | 38 | |
| Not recorded | 43 | | 51 | |
| Preradiotherapy sperm count ($\times 10^6$/mL) | | | | |
| $< 1$ | 10 | 18 | 7 | 11 |
| 1-10 | 12 | 21 | 22 | 35 |
| 11-20 | 4 | 7 | 10 | 16 |
| $> 20$ | 31 | 55 | 24 | 38 |
| Not assessed | 179 | | 179 | |

Abbreviations: WHO, World Health Organization; HCG, human chorionic gonadotropin.

### *Analysis*

Event-free times were measured from the date of randomization to the date of the event or date last known to be event-free. Event-free rates were calculated using the Kaplan-Meier method and compared using the log-rank test. All randomized patients were included in the time-to-event analyses. Acute toxicities were reported as (ordered) categorical data and were compared using $\chi^2$ tests for trend.

## RESULTS

Between July 1989 and May 1993, 478 patients were randomized by 20 centers (Appendix): 242 patients to DL radiotherapy and 236 patients to PA radiotherapy. The patient distribution was well balanced over important baseline characteristics (Table 1). Two patients, one in each arm, were technically ineligible owing to prior scrotal surgery identified after randomization (Table 2). One patient in the DL arm was erroneously treated by a PA field, and one patient requested DL-field irradiation after having been randomized for PA-field radiotherapy.

**Table 2. Treatment Deviations**

| Deviation | Reason | No. of Patients: PA Strip | No. of Patients: DL |
|---|---|---|---|
| Nonprotocol midplane dose/fractionation | | | |
| < 30 Gy | Side effects | 2 | |
| | Patient request | 1 | 4 |
| > 30 Gy | Enlarged nodes | 1 | |
| ≠ 15 fr | Doctor's error | | 2 |
| | Not recorded | | 5 |
| Prolonged treatment time | | | |
| > 22 days | Machine down-time | 3 | 8 |
| | Patient's request | 1 | 1 |
| | Bank holiday | 1 | 4 |
| | Intercurrent disease | 1 | |
| | Unknown | | 1 |
| Other | | | |
| Prior pelvic surgery identified postrandomization | | 1 | 1 |
| PA field given in error | | | 1 |
| DL field given at patient's request | | 1 | |

Abbreviation: fr, fractions.

*Radiotherapy*

The midplane dose was ≥ 22 Gy in all patients. Ninety-five percent of DL patients and 98% of PA patients received 30 Gy in 15 fractions. Owing to side effects or physician error, or on the patient's request, four patients in the PA arm and 11 patients in the DL arm received their radiotherapy by nonprotocol fractionation (most often not in 15 fractions or at a reduced midplane dose) (Table 2). In six patients from the PA arm and in 14 patients from the DL arm, the duration of treatment was prolonged beyond 22 days.

*Acute Toxicity*

During radiotherapy, nausea/vomiting, diarrhea, and, in particular, leukopenia occurred less often and were less pronounced in the PA arm than in the DL arm (Table 3).

*Relapse*

Median follow-up time is now 4.5 years, with 95% of patients having at least 2 years of follow-up and 87% having at least 3 years. A total of 18 relapses occurred between 4 and 35 months after radiotherapy, nine in each study arm (Table 4 and Fig 2). Routinely performed chest CT led to the diagnosis of relapse in three of 17 assessable cases. In five patients, clinical symptoms (pain in three patients; palpable mass in two patients) led to the diagnosis of relapse, recognized by the patient himself between two scheduled follow-up visits. In the other nine patients, the relapse was diagnosed during the routine examinations performed according to the protocol (clinical examination, chest x-ray, serum marker determinations, or abdominal CT). Biopsies of the recurrent lesions were obtained in seven patients, and all showed pure seminoma. None of the relapsing patients had elevated serum AFP levels. Two recurrences, both in patients allocated to PA radiotherapy, developed within the radiation field and measured 12 cm or more at the time of discovery; one of the these was confirmed histologically as seminoma. The relapse-free rate at 3 years was 96.0% (95% confidence interval [CI], 93.5% to 98.5%) in the PA-field group and 96.6% (95% CI, 94.2% to 98.9%) in the DL-field group (Table 5). The 95% confidence limits for the difference in relapse-free rates at 3 years were −3.4%, 4.6%; thus, an increase in the overall relapse rate in the PA field of more than 4.6% can be excluded reliably.

In four patients, all in the PA group, pelvic relapses were detected. These occurred at 7, 21, 23, and 31 months after the completion of radiotherapy, for a 3-year pelvic relapse-free rate of 98.2% (95% CI, 96.4% to 99.9%). The pelvic relapse-free rates were statistically significant at the 5% level (log-rank $P = .04$), but the 95% CI for the difference in pelvic relapse rates at 3 years is quite narrow (0% to 3.7%) and excludes an increase in pelvic relapse rates of 4% or more.

Salvage treatment comprised cisplatin/carboplatin–based chemotherapy in 17 patients; in six patients, it was combined with radiotherapy. One patient (no. 4207) underwent resection of a pulmonary metastasis as his only second treatment. One patient (no. 5412) with initial PA radiotherapy could not be salvaged and died of seminoma.

**Table 3. Acute Toxicity**

| | PA: No. | PA: % | DL: No. | DL: % |
|---|---|---|---|---|
| Nausea/vomiting, grade ($P$ for trend = .08)* | | | | |
| 0 | 69 | 30 | 59 | 25 |
| 1 | 107 | 46 | 110 | 46 |
| 2 | 32 | 14 | 28 | 12 |
| 3 | 25 | 11 | 37 | 16 |
| 4 | — | | 4 | 2 |
| Not recorded | 3 | | 4 | |
| Leukopenia, grade ($P$ for trend < .0001)* | | | | |
| 0 | 165 | 81 | 133 | 58 |
| 1 | 29 | 14 | 65 | 29 |
| 2 | 10 | 5 | 28 | 12 |
| 3 | — | | 2 | 1 |
| 4 | — | | — | |
| Not recorded | 32 | | 14 | |
| Other ($P$ = .013 for diarrhea) | | | | |
| Diarrhea | 16 | 7 | 33 | 14 |
| Dyspepsia | 5 | | 1 | |
| Erythema/acne | 3 | | 2 | |
| Colic | 1 | | | |
| Lethargy | 1 | | | |
| Epileptic cramps | | | 1 | |

*$\chi^2$ test for linear trend.

**Table 4. Relapses as of January 1, 1998**

| PA Strip Field | | | | | | DL Field | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient No. | Interval (post-XRT) (months) | Site | Maximal Diameter (cm) | First Indication of Relapse | Treatment of Relapse | Patient No. | Interval (post-XRT) (months) | Site | Maximal Diameter (cm) | First Indication of Relapse | Treatment of Relapse |
| 3201 | 14 | Supraclavicular nodes | 1.5 | Palpable neck mass | Carboplatin | 3242 | 11 | Mediastinal nodes | 4 | Clinical chest pain | Etoposide + XRT |
| 3425 | 16 | Pleural metastasis (1) | 10 | Routine chest x-ray | Carboplatin + XRT | 3454 | 16 | Lung metastases (2) | NK | Chest CT (booked in error) | BEP |
| 3634 | 23 | Right pelvis, mediastinal nodes | 2 | Palpable inguinal mass | Carboplatin + XRT | 3464 | 16 | Mediastinal nodes | "Large" | Routine chest x-ray | BEP |
| 3805 | 7 | Bone, pleura | NK | Chest x-ray | HOP + XRT | 3622 | 35 | Mediastinal nodes | NK | Chest CT | BEP |
| 3855 | 19 | Bone | NK | Hip pain | HOP + XRT | 3669 | 24 | Supraclavicular nodes | 3 | Palpable neck mass at routine visit | BEP + XRT |
| 4201 | 21 | Abdomen, right pelvis | 12 | Routine abdominal CT | BEP | 4205 | 23 | Mediastinal nodes | 5 | HCG elevated | EP |
| 4405 | 7 | Left pelvis | 4 | Elevated HCG Routine abdominal CT | Carboplatin | 4207 | 30 | Lung metastasis (1) | 2 | Chest CT | Surgery |
| 4613 | 31 | Right pelvis | 2 | Routine pelvic CT | Cisplatin | 4611 | 16 | Mediastinal nodes | 10 | Chest pain | EP |
| 5412* | 8 | Abdomen, mediastinal nodes | 14 6 | Palpable mass | EP | 5203 | 4 | Supraclavicular | 3 | No information | Carboplatin |

Abbreviations: XRT, radiotherapy; NK, not known; HOP, ifosfamide, vincristine, and cisplatin; BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin.
*Dead of seminoma.

*Overall Survival*

All patients, except one relapsing patient (from the PA arm), were salvaged by chemotherapy with or without radiotherapy, with a median postrelapse follow-up time of 3 years (range, 1.6 to 6 years). The 3-year survival rate is therefore 100% in the DL group and 99.3% (95% CI, 97.5% to 99.9%) in the PA group. The 95% CI for the difference in survival at 3 years excludes a decrease in survival in the PA group of more than 1.7%.

*Second Malignancies*

Three second cancers have been reported, two in the PA group and one in the DL group. One PA patient developed adenocarcinoma of the stomach 7 years after radiotherapy and died of cardiac arrest 5 months later. One patient in each group had a second orchiectomy for nonseminomatous tumors of the contralateral testis.

*Late Toxicity*

In 33 patients (PA field, 18 patients; DL field, 15 patients), a peptic ulcer was diagnosed at least once during follow-up. There was no clear association with treatment arm ($\chi^2$ $P$ = .54) or preradiotherapy history of peptic ulcer (Table 6). Within the first 18 months after radiotherapy, recovery of spermatogenesis was improved in the PA arm as compared with the DL arm (Table 7), in spite of the more frequent use of scrotal shielding in the DL arm (63% of DL patients *v* 3% of PA patients). In patients with normal ($> 10 \times 10^6$/mL) sperm counts preradiotherapy, the median time to the first "normal" posttreatment sperm count was 13 months for PA patients (n = 26; 95% CI, 12.5 to 13.5 months) and 20 months for DL patients (n = 23; 95% CI, 12.5 to 30 months). In those with abnormal ($\leq 10 \times 10^6$/mL) sperm counts preradiotherapy, the median time to the first normal sperm count was 24 months for PA patients (n = 10; 95% CI, 9 to 39 months) and 37 months for DL patients (n = 21; 95% CI, 15 to 60 months). Time to first normal postradiotherapy sperm count ($> 10 \times 10^6$/mL) was significantly longer in the DL group (log-rank test stratified for normal/abnormal preradiotherapy count, $\chi^2 = 6.15$; $P = .01$). However, the difference declined with continued follow-up, and at 3 years from the start of radiotherapy, an estimated 92% of DL patients had attained a sperm count of at least $10 \times 10^6$/mL.

## DISCUSSION

Although several institutions have introduced a surveillance policy for patients with testicular seminoma stage I,[14-18] adjuvant radiotherapy remains the routine treatment of choice.[18] Contrary to the situation in nonseminoma patients, recurrences after 3 to 5 years are not uncommon in seminoma patients. Therefore, a surveillance policy in these patients requires long-term patient compliance and sufficient health care resources for follow-up. Furthermore, as no useful serum marker is available for patients with seminoma, the frequent and prolonged performance of clinical examinations and of abdominopelvic CT examinations is a condition sine qua non for the surveillance policy in seminoma patients. In most cases, such CT examinations are done twice yearly for the first 5 years. Experience suggests that the above conditions are not always fulfilled in the routine clinical setting. Therefore, surveillance is regarded as experimental by most institutions, whereas abdominal radiotherapy has maintained its role as standard adjuvant treatment in stage I seminoma.

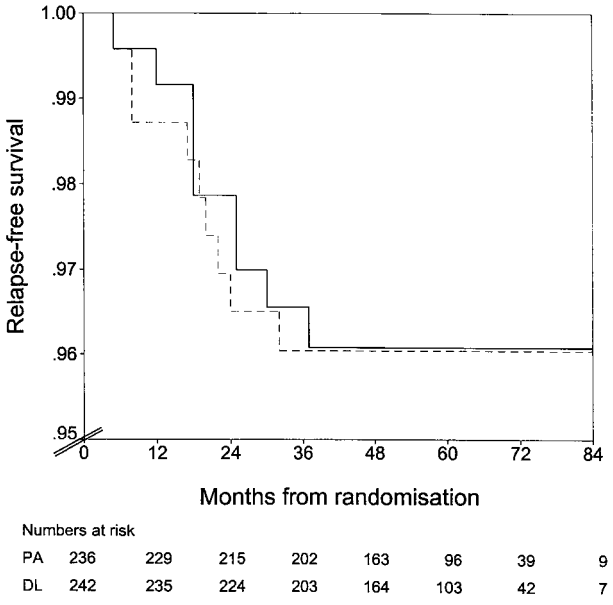


**Fig 2. Relapse-free survival rates by allocated treatment. - - - -, PA field; ——, DL field.**

Our results and also those from other studies[22,23] indicate that PA radiotherapy is as safe as DL radiotherapy in patients with seminoma stage I and undisturbed testicular lymph drainage with regard to overall survival, which approaches 100% in both arms. However, because pelvic recurrences are more frequent after PA than after DL radiotherapy and may occur several years after treatment, these beneficial results are obtained only if the patient undergoes follow-up for at least 5 years, with the regular performance of abdominal and pelvic CT examinations. Although the optimal frequency of follow-up examinations and abdominopelvic CTs remains unknown, both for patients following the surveillance policy and for those receiving radiotherapy, our irradiated patients have followed a less intensive follow-up schedule than described in the literature for surveillance patients. Fewer CT examinations and fewer outpatient visits in the irradiated patients imply an easier, although safe, follow-up than is offered to surveillance patients. However, the fact that two ''in-field'' abdominal recurrences were at least 12 cm in size at their diagnosis indicates that, irrespective of the radiotherapy field, the interval between two CT examinations should perhaps be shortened.

**Table 5. Outcome**

| | Treatment Field | |
|---|---|---|
| | PA (%) | DL (%) |
| Relapse-free survival | | |
| Time from randomization, years | | |
| 1 | 98.7 | 99.2 |
| 2 | 96.5 | 97.4 |
| 3 | 96.0 | 96.6 |
| 95% CL | 93.5, 98.5 | 94.2, 98.9 |
| Difference in 3-year relapse-free survival rate = 0.6 (−3.4, +4.62) | | |
| Pelvic relapse-free survival ($P$ = .04) | | |
| 3-year | 98.2 | 100 |
| 95% CL | 96.4, 99.9 | 98.2, 100 |
| Difference in 3-year pelvic relapse-free survival rate = 1.8 (0, 3.7) | | |
| Overall 3-year survival | | |
| 3-year | 99.3 | 100 |
| 95% CL | 97.5, 99.9 | 98.2, 100 |
| Difference in 3-year survival rate = 0.7 (0.3, 1.7) | | |

Abbreviation: CL, confidence limits.

**Table 6. Peptic Ulcer During Treatment and/or Follow-Up**

| Pretreatment Ulcer | Ulcer During/Posttreatment | | | |
|---|---|---|---|---|
| | PA Strip | | DL | |
| | No | Yes | No | Yes |
| No | 212 | 16 (7%) | 219 | 15 (6%) |
| Yes | 2 | 2 | 3 | 0 |
| Not recorded | 4 | 0 | 5 | 0 |
| Total | 216 | 18 (8%) | 227 | 15 (6%) |

PA radiotherapy offers several advantages as compared with DL irradiation:

*Field Set-Up*

During the daily radiotherapy sessions, the set-up of a PA field requires about 65% of the time necessary to set up a DL field (unpublished observations). In a busy radiotherapy department, even these few minutes spared during individual treatment sessions contribute to an improved flow of patients. Furthermore, the rectangular PA fields are associated with more reliable product ability and higher technical accuracy than the DL fields, which require the use of lead blocks.

*Acute Toxicity*

PA radiotherapy has a bone marrow–sparing effect, compared with DL radiotherapy, and is associated with less acute gastrointestinal toxicity, although the differences were less pronounced than expected during the planning phase of the trial. Although the clinical significance of moderately re-

**Table 7. Postradiotherapy Recovery of Spermatogenesis**

| | Treatment Arm* | | | |
|---|---|---|---|---|
| | PA Strip (n = 54) | | DL (n = 48) | |
| | No. | % | No. | % |
| Maximal sperm count ($\times 10^6$/mL) in first 18 months | | | | |
| > 10 | 32 | 59 | 18 | 38 |
| 1-10 | 16 | 30 | 13 | 27 |
| < 1 | 6 | 11 | 17 | 35 |
| Median age, years | 34 | | 31 | |
| Scrotal shielding | 3 | | 35 | |

*$\chi^2$ (trend) $P <$ .001.

duced leukopenia is not clear in these patients, the reduction of nausea/vomiting and diarrhea during radiotherapy undoubtedly represents a clinical benefit.

*Improved Spermatogenesis*

Another advantage of PA radiotherapy as compared with DL irradiation is the considerable reduction of the testicular irradiation dose. This has been shown in an experimental setting[22] to limit reduction of spermatogenesis. These previous observations are confirmed in the present study by significantly higher sperm counts throughout the follow-up period, but particularly in the first 2 years after PA rather than DL radiotherapy. Although this difference in sperm counts lessened toward the end of the second year, owing to recovery of sperm cell production in the DL arm, the fertility-saving effect of PA radiotherapy may be of clinical significance in seminoma patients, who present with a median age of 38 years: If they (still) plan to have children posttreatment, most of the patients (and their partners) do not want to delay paternity for several years. Furthermore, the spermatogenesis-saving effect may be of particular benefit in patients with pre-existing oligospermia and elevated serum follicle-stimulating hormone. These combined findings may indicate a more profound disturbance of the sperm cell production in the remaining testicle and reduced ability of recovery after irradiation.[23-25]

*Peptic Ulcer*

Both treatments confer a similar risk of posttreatment peptic ulcer. The present study could not confirm previous observations of an increased incidence of peptic ulcer in patients with a history of peptic ulcer or bowel operations.[8,26] If the development of this complication is dependent on the midplane dose, the risk should be decreased in patients receiving midplane doses of less than 30 Gy.

*Second Non-Germ Cell Cancer*

The time of follow-up is still too short for assessment of any risk-reducing effect of PA radiotherapy. Observation times of 10 to 20 years will be necessary to make meaningful statements. PA radiotherapy, which excludes the pelvic area from the irradiation field, may reasonably be expected to reduce the risk of radiation-induced bladder cancer and pelvic sarcoma, which have been demonstrated in previous studies.[9,10,25,27]

The MRC is continuing to investigate alternative treatments for these patients and has recently completed a randomized trial (TE18) in which over 600 patients were randomized to either 30 Gy in 15 fractions (the schedule used here) or to 20 Gy in 10 fractions. Another ongoing MRC trial (TE19), conducted in collaboration with the European Organization for Research and Treatment of Cancer, randomizes patients to radiotherapy or one course of single-agent carboplatin to assess relapse rates, morbidity, and quality of life on both treatments. Although the results of these studies are not yet available, the present study shows that PA radiotherapy can be adopted as routine treatment in patients with seminoma stage I with an undisturbed testicular lymph drainage, provided that long-term CT-based follow-up is established. The overall 3-year survival rate is equivalent to that after DL radiotherapy, although there is an increased risk for pelvic relapses. The main advantage of PA radiotherapy is the reduced acute/subacute hematologic, gastrointestinal, and gonadal toxicity (and possibly a reduced risk of second malignancies).

## APPENDIX
### Participating Clinicians

| Clinician | Hospital | No. of Patients |
|---|---|---|
| Professor SD Fosså | Norwegian Radium Hospital, Oslo, Norway | 75 |
| Professor A Horwich / Dr DP Dearnaley | Royal Marsden Hospital, Sutton | 69 |
| Dr JM Russell | Western Infirmary, Glasgow | 30 |
| Dr JT Roberts | Newcastle General Hospital, Newcastle | 24 |
| Dr MH Cullen | Queen Elizabeth Hospital, Birmingham | 20 |
| Dr NJ Hodson | Royal Sussex County Hospital, Brighton | 20 |
| Dr WG Jones | Cookridge Hospital, Leeds | 19 |
| Dr H Yosef | Western Infirmary, Glasgow | 17 |
| Dr G Duchesne | Middlesex Hospital, London | 16 |
| Dr JR Owen | Cheltenham General Hospital, Cheltenham | 14 |
| Dr EJ Grosch | Mount Vernon Hospital, Northwood | 11 |
| Dr AD Chetiyawarda | Queen Elizabeth Hospital, Birmingham | 10 |
| Dr NJ Reed | Western Infirmary, Glasgow | 10 |
| Dr DJ Cole | Churchill Hospital, Oxford | 9 |
| Dr A Harnett | Western Infirmary, Glasgow | 9 |
| Dr J Glaholm | Queen Elizabeth Hospital, Birmingham | 7 |
| Dr AL Houghton | Northampton General Hospital, Northampton | 7 |
| Dr J Mould | Queen Elizabeth Hospital, Birmingham | 7 |

Appendix (Cont'd)

| Clinician | Hospital | No. of Patients |
|---|---|---|
| Professor NM Bleehen | Addenbrookes Hospital, Cambridge | 6 |
| Dr RD Errington | Clatterbridge Hospital, Wirral | 6 |
| Dr S Myint | Clatterbridge Hospital, Wirral | 6 |
| Dr J Graham | Bristol Oncology Centre, Bristol | 5 |
| Dr A Stockdale | Walsgrave Hospital, Coventry | 5 |
| Dr MV Williams | Addenbrookes Hospital, Cambridge | 5 |
| Dr PA Canney | Belvidere Hospital, Glasgow | 4 |
| Dr D Fermont | Mount Vernon Hospital, Northwood | 4 |
| Dr D Mahy | Cheltenham General Hospital, Cheltenham | 4 |
| Dr GH Newman | Bristol Oncology Centre, Bristol | 4 |
| Dr D Spooner | Queen Elizabeth Hospital, Birmingham | 4 |
| Dr B Cottier | Clatterbridge Hospital, Wirral | 3 |
| Dr AC Jones | Churchill Hospital, Oxford | 3 |
| Dr RW Laing | Churchill Hospital, Oxford | 3 |
| Dr H Lucraft | Newcastle General Hospital, Newcastle | 3 |
| Professor MJ Mason | Velindre Hospital, Cardiff | 3 |
| Dr CS Paine | Churchill Hospital, Oxford | 3 |
| Dr J Bozzino | Newcastle General Hospital, Newcastle | 2 |
| Dr AM Branson | Newcastle General Hospital, Newcastle | 2 |
| Dr PI Clark | Clatterbridge Hospital, Wirral | 2 |
| Dr TR Habeshaw | Belvidere Hospital, Glasgow | 2 |
| Dr FR Macbeth | Western Infirmary, Glasgow | 2 |
| Dr EJ Maher | Mount Vernon Hospital, Northwood | 2 |
| Dr A Slater | Clatterbridge Hospital, Wirral | 2 |
| Dr D Whillis | Raigmore Hospital, Inverness | 2 |
| Dr EC Whipp | Bristol Oncology Centre, Bristol | 2 |
| Dr CS Askill | Singleton Hospital, Cardiff | 1 |
| Dr A Cassoni | Middlesex Hospital, London | 1 |
| Dr P Dyson | Cumberland Infirmary, Carlisle | 1 |
| Dr TR Evans | Newcastle General Hospital, Newcastle | 1 |
| Dr S Goodman | Bristol Oncology Centre, Bristol | 1 |
| Dr MJ Hughes | Clatterbridge Hospital, Wirral | 1 |
| Dr RD Jones | Belvidere Hospital, Glasgow | 1 |
| Dr D Kerr | Belvidere Hospital, Glasgow | 1 |
| Dr McGurk | Belvidere Hospital, Glasgow | 1 |
| Dr A Phillips | Charingcross Hospital, London | 1 |
| Dr T Priestman | Queen Elizabeth Hospital, Birmingham | 1 |
| Dr R Rampling | Western Infirmary, Glasgow | 1 |
| Dr NJ Rowell | Churchill Hospital, Oxford | 1 |
| Professor M Saunders | Mount Vernon Hospital, Northwood | 1 |
| Dr WG Steward | Belvidere Hospital, Glasgow | 1 |

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