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ORIGINAL ARTICLE

Adjuvant radiotherapy in stage I seminoma: Is there a role for further reduction of treatment volume?

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Abstract
An analysis was performed to determine whether a cranial reduction of the portals to the T11/T12 junction instead of the common T10/T11 junction would alter the outcome of patients with stage I seminoma. Of 163 consecutive patients with newly diagnosed testicular seminoma referred to the authors' institution between April 1992 and April 1999, 80 patients with stage I seminoma were treated with cranially reduced para-aortic treatment fields reaching from the top of T12 to the bottom of L4. Median total dose was 20.0 Gy (range, 19.8–27.2 Gy). Patients were followed-up by the use of CT in regular intervals. After a median follow-up of 7.1 years (range, 4.1–11.1 years), four patients (5%) had relapsed resulting in an actuarial 5-year relapse-free survival of 95%. No patients relapsed within the cranially reduced treatment volume above the top of T12. The cranial reduction of the para-aortic treatment fields resulted in a median reduction of treatment volume of 16% (range, 13–21%). The achieved median reduction in treatment volume of 16% appears to be relevant and is not associated with an increased relapse rate. This approach is recommended in analogy to the surgical approach in NSGCT to further minimize the risk of radiation-related late effects.

Introduction

Seminoma accounts for about 40% of testicular cancer and tends to occur in slightly older patients than those with non-seminomatous germ cell tumors (NSGCT). The majority of patients present with stage I disease, i.e. without evidence of regional lymph node involvement. Because of the high radiosensitivity and its predictable pattern of spread to the para-aortic lymph nodes, adjuvant radiotherapy (RT) of stage I seminoma following ipsilateral orchiectomy achieves long-term relapse-free survival as high as 95% and cancer-specific survival of approximately 98% [1]. Alternative management strategies such as surveillance or adjuvant chemotherapy have been investigated for stage I seminoma with the aim of reducing the infrequent but recognized toxicities associated with adjuvant RT [2,3].

In the last decade several clinical trials intended to reduce the dose and extent of adjuvant radiotherapy in stage I disease have been undertaken. The strategy of all these trials has been to minimize possible treatment-related morbidity while leaving the excellent cure rate unchanged [4]. A British randomized prospective trial of the Medical Research Council (MRC) [5] and a German prospective multicenter trial [6] investigated the limitation of adjuvant RT to para-aortic fields only. The authors found similar survival rates in comparison with portals previously used comprising the para-aortic region and the ipsilateral iliac lymph nodes, described as dog-leg fields. Since then, para-aortic fields have been recommended as standard treatment volume for adjuvant RT of stage I seminoma [5]. Although most radiation oncologists choose similar para-aortic fields with the cranial border placed on the top of T11, this cranial border remains questionable since the upper limit of retroperitoneal lymphadenectomy in low-stage NSGCT has been placed on the level of the renal vessels projecting on L1/L2 [7,8].

We report here on our single institution experience on adjuvant para-aortic radiotherapy in stage I seminoma with cranial reduction of field borders by one thoracic vertebra from the top of T11 to the

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top of T12 in order to elucidate the possible role of further reduction of para-aortic treatment volume in stage I seminoma in terms of safety and treatment efficacy.

Material and methods

Patient characteristics

Between April 1992 and April 1999, 163 consecutive patients with newly diagnosed testicular seminoma were referred to our department; 106 of these patients had stage I disease according to the TNM classification of malignant tumors from 1997 [9] and a minimum follow-up of four years. No patient had a history of prior radiotherapy. The staging included CT scans of the thorax, abdomen, and pelvis. Serum AFP and -human chorionic gonadotropin (β-hCG) levels were analyzed prior to and following orchiectomy in the case of an elevated β-hCG level. Informed consent was obtained from each patient including information concerning alternative therapy strategies.

Twenty-six (25%) patients with stage I seminoma were irradiated with fields other than investigated here for different reasons and were excluded from this analysis: Four patients received radiotherapy with dog-leg fields; 12 patients were treated with para-aortic fields only without cranial field reduction. Five of these 16 patients had a history of contralateral NSGCT; another two patients had a history of inguinal surgery due to maldescent of testis. Seven patients opted for surveillance strategy as an alternative treatment option. One patient terminated radiotherapy on his own decision after 10.8 Gy (6 fractions) without further comment. Finally, two patients have been lost to follow-up after 1.8 and 2.4 years and were subsequently excluded from this analysis. Both were disease-free at their last follow-up.

The remaining 80 patients were treated with cranially reduced para-aortic treatment fields and comprise the study collective of this analysis (Figure 1). Median age was 35.3 years (range, 19.2–65.7 years). Median interval between orchidectomy and radiotherapy was 3.9 weeks (range, 1.1–8.0 weeks). The tumor size ranged from 1.0 to 9.0 cm with a median value of 3.5 cm. No patient had involvement of the spermatic cord or the scrotum. Further characteristics are given in Table I. In nine patients (11%) additional testicular intraepithelial neoplasia (TIN) was present in the ipsilateral testis. Contralateral TIN was found in two patients, each combined with simultaneous ipsilateral TIN. Both patients received additional radiotherapy directed to the contralateral testis using

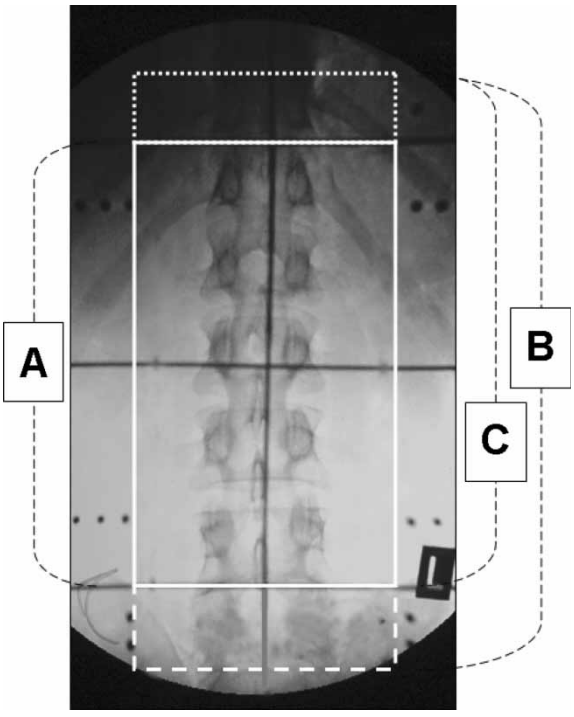

Figure 1. Simulator x-ray film showing the different target volumes used in this study (A), MRC trial (B) [22], and German trial (C) [6].

electrons (10 × 2.0 Gy). Eight patients presented with preoperatively elevated serum β-hCG levels while serum AFP levels were in the normal range. All β-hCG levels returned to normal postoperatively.

Radiotherapy and treatment volume

Linac-based radiotherapy was delivered to the para-aortic region by ap/pa opposing fields with 10 MV or 23 MV photons. The upper field border reached from the top of thoracic vertebra 12 (T12) to the lower border of the lumbar vertebra 4 (L4), as shown in Figure 1. The lateral field borders included the transverse processes of the lumbar vertebrae, resulting in a field width between 9 and 11 cm. In 10 patients with left-sided seminoma ipsilateral renal pelvis was included by individually shaped field borders. CT-based treatment planning (10 mm slice thickness) was performed in all patients. The setup of treatment field was verified by commercially available portal films. The median central midplane dose was 20 Gy (range, 19.8 to 27.2 Gy), and was applied in daily fractions of 1.6 to 2.0 Gy (median, 1.7 Gy), five times a week.

Follow-up

Patients were followed by their urologists at regular intervals every three months for the first two years following adjuvant radiotherapy, every four months

Table I. Characteristics of the 80 patients included in this analysis.

Variable	Number of patients without relapse (n = 76)	Number of patients with relapse (n = 4)
Age		
≤36 years	37	3
>36 years	39	1
Testis involved		
Left-sided	37	2
Right-sided	38	2
Bilateral	1	0
Prior inguinal surgery	6	0
Elevated β-hCG level preoperatively	8	0
Tumor size		
≤4 cm	47	1
>4 cm	29	3
Rete testis invasion		
Absent	55	3
Present	20	1
Vascular space invasion		
Absent	75	3
Present	1	1
Lymphatic space invasion		
Absent	74	4
Present	2	0
Tunica vaginalis invasion		
Absent	73	0
Present	3	0
TIN		
None	67	4
Ipsilateral	9	0
Contralateral	2	0

in the third year, and every six months thereafter. Follow-up included clinical examination and determination of tumor marker. Abdominal and pelvic CT scans were taken on a six-month basis for the first two years and once a year thereafter. Treatment-related late effects were evaluated according to the EORTC/RTOG scores [10]. In case of relapse, CT scans were compared with the initial simulator and verification films as well as the planning CT scans of the same patient to determine the site of relapse in relation to the treatment fields.

Statistical analysis

Relapse-free survival was calculated as the time interval between end of radiotherapy and the first occurrence of relapse. Patients alive without evidence of disease were censored at the date of their last follow-up. Relapse-free and disease-specific survival was calculated by the method of Kaplan–Meier using a commercially available statistical software package (SPSS for Windows, Version 10.5).

Results

After a median follow-up of 7.1 years (range, 4.1 to 11.1 years), four patients had developed lymph node recurrence, resulting in an actuarial 5-year relapse-free survival of 95% (Figure 2). One 57 year-old patient had died 5.2 years after radiotherapy without evidence of disease.

Median time to relapse was 18.5 months (range, 9–47 months) after RT. In all four patients the relapse was confirmed by biopsy. The characteristics of these patients are given in Table II and illustrated in Figure 3. Three patients had nodal relapses within the ipsilateral pelvis and outside the para-aortic treatment fields. One of these patients (A.K.) presented with additional systemic dissemination.

It is noteworthy that 9 months after 19.8 Gy of adjuvant RT one patient (B.H.) developed a solitary lymph node metastasis below the ipsilateral renal vessels on the left side, undoubtedly lying within the para-aortic treatment fields. This patient had received long-term immunosuppressive therapy following kidney transplantation 13 years and again four months prior to the diagnosis of seminoma. A re-evaluation of the initial CT scans did not reveal para-aortic lymph node enlargement at the time of adjuvant RT. It is important to note that no relapses occurred within the cranially reduced treatment

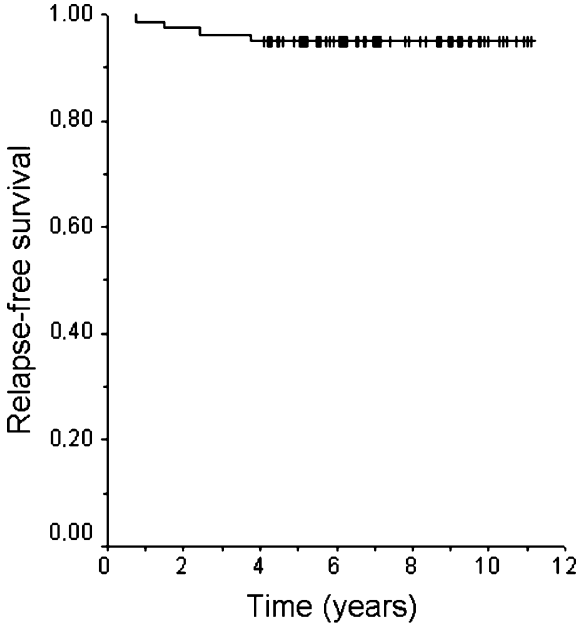

Figure 2. Relapse-free survival of 80 patients with seminoma stage I irradiated adjuvantly with cranially reduced para-aortic fields.

Table II. Clinical characteristics of relapsing patients.

Patient	Age (years)	Initial tumor size and further risk factors	Interval to relapse (months)	Site of relapse	Treatment of relapse	Outcome NED (years)
A.K. (Triangle)	41.4	9.0 cm; RTI	18	Ipsilateral pelvis and disseminated	4 × PEI	5.7
G.K. (Square)	28.8	7.5 cm;V1	47	Pelvis and inguinal Ln (ipsilateral)	4 × PEB	4.5
F.R. (Rhombus)	32.6	6.8 cm	19	Bilateral pelvis	4 × PEI	7.5
B.H. (Circle)	25.5	3.5 cm	9	Ipsilateral para–aortic Ln (in field)	4 × Carbo	6.6

Abbreviations: RTI = rete testis invasion; V = vascular invasion; Ln = lymph node(s); PEI = cisplatin, etoposide, and ifosfamide; PEB = cisplatin, etoposide, and bleomycin; Carbo = carboplatin; NED = no evidence of disease.

volume (above the top of T12). All relapsing patients were successfully salvaged by chemotherapy with no evidence of recurrent disease after a median follow-up of 6.2 years.

The cranial reduction of the treatment fields from the top of T11 to the top of T12 resulted in a median reduction of the cranio-caudal field length of 2.7 cm (range, 2.0 to 3.4 cm) corresponding to a median reduction of treatment volume of 16% (range, 13% to 21%) as illustrated in Figure 4.

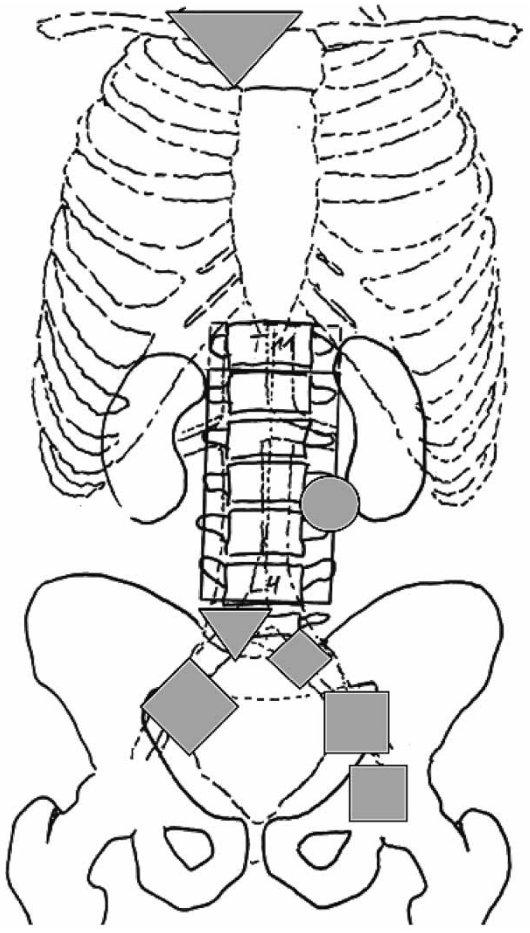

Figure 3. Illustration of the patterns of relapse of the four patients presented in Table II.

Discussion

The high overall cure rates in stage I seminoma, historically treated with radical orchidectomy and postoperative radiation therapy (RT), have raised controversies regarding the optimal therapy for this tumor entity in terms of radiation dose and the appropriate choice of treatment volumes [11]. Several clinical trials have aimed at limitation of dose and extent of adjuvant radiotherapy in stage I disease in order to further reduce the already low incidence of late treatment-related morbidity while leaving the excellent cure rate unchanged [12–14]. Special interest has been focused on minimizing the scatter dose to the remaining testis leading to treatment volumes confined to the para-aortic lymph nodes [5,6]. In contrast with the lower field borders the upper border of the para-aortic fields at the T10/T11 level has not been questioned by radiation oncologists so far although the surgical approach

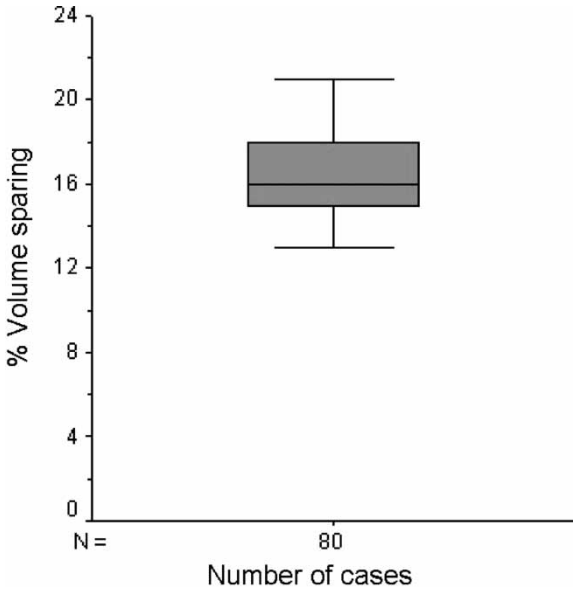

Figure 4. Box-plot diagram of treatment volume sparing in this analysis.

of retroperitoneal lymphadenectomy in germ cell tumors has changed over time.

The important MRC trial [5] investigated the limitation of the radiation treatment volume. More than 400 patients with stage I seminoma were randomized to receive 30 Gy to the para-aortic region with or without inclusion of the ipsilateral iliac lymph nodes (dog-leg fields). No difference in 3-year relapse-free survival and overall survival could be found among the two treatment arms. However, patients treated with para-aortic fields only exhibited significant lower late morbidity, albeit at the expense of a non-significantly increased rate of pelvic recurrence. The authors [5] concluded that para-aortic field irradiation alone with portals reaching from T11/T12 to the L5/S1 junction should be regarded as the standard adjuvant therapy in stage I seminoma (see Figure 1).

A prospective non-randomized German trial [6] treated the para-aortic region with 26 Gy and found comparable results with 4-year disease-specific and relapse-free survival of 99.8% and 95.8%, respectively. It is of note that in this German trial the lower field border differed from that of the MRC trial by reaching to the L4/L5 junction only (see Figure 1), which has been established widely in clinical practice in Germany since then [15].

The extent of the upper field border to the top of T11 in adjuvant RT of stage I seminoma has historically been based on patterns of lymphatic spread in testicular cancer, which had been analyzed in large lymphadenectomy and lymphangiographic studies [16–19]. But the extent of surgical lymph node dissection has changed over time, primarily due to the results of extensive mapping studies by Donohue et al. in the 1970s [20]. In case of retroperitoneal lymph node metastasis of more than 2 cm in diameter in NSGCT, a complete bilateral retroperitoneal lymph node dissection (RPLND) has to be performed including bilateral suprahilar areas below the inferior mesenteric artery, whereas in lower stage 1 NSGCT, a RPLND without extensive suprahilar dissection seems to be sufficient [7]. Thus, RPLND does not exceed the level of renal vessels cranially projecting onto the top of L1. This surgical approach significantly reduces postoperative morbidity without compromising the high cure rate in stage I NSGCT [8,21].

Assuming similar patterns of lymphatic spread in seminomatous compared with non-seminomatous germ cell tumors, the strategies in the treatment of NSGCT may serve as a basis for the treatment in seminomas as well. As a consequence the extent of the upper field border of adjuvant radiotherapy in stage I seminoma needs to be further clarified as at least stray irradiation may irradiate the heart. To our knowledge there is only one single publication on adjuvant radiotherapy in stage I seminoma available reporting on cranially reduced field borders as low as the top of L1 [12]. Kiricuta et al. [12] treated 86 patients with stage I seminoma with portals reaching from the top of L1 to the bottom of L5 and a median total dose of 30 Gy. After a median follow-up of 63 months four patients had relapsed, all outside the para-aortic region.

The results of our analysis with an actuarial 5-year relapse-free rate of 95% compares favorably with those reported by others [6,12–14,22]. It is important to note that no patient in our series relapsed within the cranially reduced treatment volume (above the top of T12). However, the 95% confidence interval of an observation of 0 among 80 patients indicates that there still might be 4.5% local recurrence within the 95% confidence limit of this series. On the other hand, a disease-specific survival rate of 100% has been achieved as a result of highly efficient salvage chemotherapy in patients experiencing treatment failure after adjuvant radiotherapy.

Besides reduction in treatment volume our results support the safety of dose reduction in the adjuvant setting, which had been addressed in a randomized MRC trial comparing 20 Gy in 10 fractions with 30 Gy in 15 fractions to the para-aortic region only. After a median follow-up of 5 years equivalent relapse rates were found in both arms [22,23].

Interestingly, one of our patients presented with an in-field lymph node relapse just below the ipsilateral renal vessels 9 months after 19.8 Gy of adjuvant para-aortic field RT. This patient has been on long-term immunosuppressive therapy following repeated kidney transplantations prior to the diagnosis of seminoma. Although definitive conclusions cannot be drawn from one single case, 20 Gy may well represent the threshold dose to control effectively microscopic disease in stage I seminoma. When reducing total doses below the level of 20 Gy one might probably just as well assign the patient to a surveillance strategy with RT reserved as a salvage treatment. This may equally be derived from the recently published results of the German Testicular Cancer Study Group (GTCSG) dose-reduction trial for testicular intraepithelial neoplasia (TIN). In this trial the lowest dose to control TIN effectively was found to be 18 Gy [24].

In the analysis presented here the top of L5 was chosen as the lower field border in accordance with the German Testicular Cancer Study Group (GTCSG) (see Figure 1). However, in the randomized MRC studies the lower field border was placed at the L5/S1 level. From the evidence-based point of view, the results of the MRC trial as the only volume reduction trial support the use of L5/S1 as

the lower field border, although the scatter dose to the remaining testis is increased compared with the L4/L5 level [25]. The equivalence of L5/S1 compared with L4/L5 in terms of disease-specific and relapse-free survival will probably never be tested owing to the large number of patients required and the increasing use of alternative treatment options.

A surveillance strategy is such an alternative treatment option particularly in low-risk patients, although good compliance and adequate long-term follow-up are essential. Several risk factors predictive of relapse have been described so far. In a pooled analysis of four large surveillance studies Warde et al. [26] identified size of primary tumor and rete testis invasion as the most important predictive factors for relapse in patients with stage I seminoma managed with surveillance. This information will allow patients and clinicians a more accurate assessment of an individual patient's risk of relapse, i.e. patients who belong to the high-risk group should be offered adjuvant treatment. A prospective trial of the German Testicular Cancer Study Group using such a risk-adapted strategy is under way [2].

An alternative to surveillance alone is the use of adjuvant chemotherapy, which has been demonstrated to be effective in stage I nonseminoma [27]. But this approach is still experimental in stage I seminoma because there have been only a few reports of chemotherapy use so far. Initial clinical results with one cycle of carboplatin were promising with a relapse rate lower than 1% after a median follow-up at least of 44 months [28]. Meanwhile the publication by Dieckmann et al. [29] reporting on a relapse rate of 8.6% in 93 patients, followed up for a median of 4 years after a single course of adjuvant carboplatin in stage I seminoma, may serve as a reminder to use this treatment approach cautiously; however, the dose may have been suboptimal [11]. Steiner et al. [30] treated 108 patients with two cycles of carboplatin, and with mean follow-up of 5 years, there were only two relapses. However, the prospective randomized multicenter trial of the MRC/EORTC intergroup comparing one course of single-agent carboplatin AUC 7 with para-aortic RT (optionally 20 Gy or 30 Gy) has now been closed after inclusion of 1 447 patients with preliminary results presented recently at the 2004 ASCO Annual Meeting [31]: relapse-free survival rates for radiotherapy vs. chemotherapy were 96.6% (95%CI: 95.2% to 97.6%) vs. 95.4% (93.3% to 96.9%) at 3 years (HR 1.39; 90%CI: 0.92 to 2.11; $p = 0.195$). With a median follow-up of 3 years, an absolute increase in the relapse rate in the chemotherapy arm of more than 4% at 3 years could be excluded reliably. The pattern of relapse differs: more retroperitoneal lymph node relapse with carboplatin (70% vs. 7%) versus more pelvic lymph node relapse with adjuvant RT (28% vs. 4%). Early data on second malignancies favoured the chemotherapy group: second germ cell tumours have been reported in 3 patients with chemotherapy vs. 11 with RT. The reduction of contralateral testis tumour (2 versus 10 patients) could offer further advantages over a full course of RT. Further follow-up is needed to confirm that these results are maintained beyond 3 years. Nevertheless, the trial provides level 1 evidence supporting a further treatment option for patients with stage I seminoma [31,32].

In conclusion we could demonstrate that adjuvant para-aortic RT with cranially reduced field borders by one vertebra is a safe and effective treatment strategy in the management of patients with stage I seminoma. The achieved median reduction in treatment volume of 16% appears to be relevant and was not associated with an increased relapse rate. We recommend this approach in analogy to the surgical approach in NSGCT to further minimize the risk of radiation-related late effects.

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