Radiotherapy for Stages IIA/B Testicular Seminoma: Final Report of a Prospective Multicenter Clinical Trial

By Johannes Classen, Heinz Schmidberger, Christoph Meisner, Rainer Souchon, Marie-Luise Sautter-Bihl, Rolf Sauer, Stefan Weinknecht, Kai-U. Köhrmann, and Michael Bamberg

Purpose: **A prospective multicenter trial was initiated to evaluate the role of modern radiotherapy with reduced treatment portals for stage IIA and IIB testicular seminoma.**

Patients and Methods: **Patients with stages IIA/B disease (Royal Marsden classification) were assessable for the trial. Staging comprised computed tomography of the chest, abdomen, and pelvis as well as analysis of tumor markers alpha-fetoprotein and beta human chorionic gonadotropin. Linac-based radiotherapy was delivered to para-aortic and high ipsilateral iliac lymph nodes. The total doses were 30 Gy for stage IIA and 36 Gy for stage IIB disease.**

Results: **Between April 1991 and March 1994, 94 patients were enrolled for the trial by 30 participating centers throughout Germany. Seven patients were lost to follow-up. Median time to follow-up of 87 assessable patients was 70 months. There were 66 stage IIA and 21 stage IIB patients. One mediastinal and one field-edge relapse were observed in the stage IIA group. In the stage IIB group, there was one mediastinal and one mediastinal/pulmonary relapse. All patients were treated with a salvage regimen of platinum-based chemotherapy. Actuarial relapse-free survival at 6 years was 95.3% (95% confidence interval [CI], 88.9% to 100%) and 88.9% (95% CI, 74.4% to 100%) for stage IIA and IIB groups, respectively. Maximum acute side effects were 8% grade 3 nausea for stage IIA and 10% grade 3 nausea and diarrhea for stage IIB groups. No late toxicity was observed.**

Conclusion: **Radiotherapy for stages IIA/B seminoma with reduced portals yields excellent tumor control at a low rate of acute toxicity and no late toxicity, which supports the role of radiotherapy as the first treatment choice for these patients.**

J Clin Oncol 21:1101-1106. *© 2003 by American Society of Clinical Oncology.*

APPROXIMATELY 45% to 50% of testicular cancer patients are diagnosed with pure seminoma, the majority of which have early stage I disease. Only 10% to 15% of the patients present with clinical stage IIA or IIB seminoma with limited retroperitoneal lymph node metastases, and less than 5% have more advanced disease with bulky retroperitoneal metastases or distant tumor spread. During the last decades, radiotherapy has been the mainstay of treatment in stage II seminoma for patients with limited lymph node involvement. The rationale for radiotherapy is the high radiosensitivity of seminoma and the stepwise dissemination of tumor cells via the lymphatic system in the retroperitoneum. This highly predictive tumor spread provides the basis for target volume definition of radiotherapy on the basis of anatomic land marks. Traditionally, treatment portals for stage II seminoma comprise pathologically enlarged lymph nodes with a safety margin and one adjacent echelon. This principle of target volume definition has led to typical field arrangements for radiotherapy with an inverted Y for infradiaphragmatic irradiation covering para-aortic and bilateral iliac lymph nodes. For treatment of the supradiaphragmatic echelon, the left-sided supraclavicular region and the mediastinum were frequently irradiated to eradicate subclinical disease. However, extended-field irradiation for seminoma conflicts with the risk of late morbidity affects on the cardiovascular[1] and hematopoietic system and the possible increased risk of radiation-induced second malignancies.[2]

With the availability of potent salvage chemotherapy regimens, prophylactic mediastinal or supraclavicular irradiation has been abandoned in most radiotherapy centers. Likewise, contralateral iliac treatment has been omitted in many institutions to limit treatment-related toxicity. Because of the low incidence of stage II seminoma, however, available reports on radiotherapy are limited by small patient numbers and long, mostly retrospective periods of patient accrual. Consequently, there is a lack of homogeneity in most study populations with respect to staging and treatment techniques applied. Thus reported relapse rates vary widely, with 0% to 12.5% for stage IIA[3,4] and 0% to 25% for stage IIB disease.[4,5] Furthermore, there is a lack of series reporting treatment outcome for patients staged and treated according to current standards of care. Therefore, we initiated a prospective multicenter trial for radiotherapy of stage IIA and IIB seminoma as defined by the Royal Marsden classification.[6] We decided to further reduce the treatment target volume by limiting the lower field border to the level of the upper rim of the ipsilateral acetabulum, thus including only lymph nodes along the common iliac vessels as opposed to most other series that used mid obturator foramen or bottom of the obturator foramen as landmark for lower field border definition. The aim of the trial was to prospectively assess relapse rates as well as acute and late toxicity of irradiation with limited volume treatment. Interim

From the Departments of Radiation Oncology and Medical Information Processing, University of Tübingen, Tübingen; Department of Radiation Oncology, University of Göttingen, Göttingen; Department of Radiation Oncology, Allgemeines Krankenhaus Hagen, Hagen; Department of Radiation Oncology, Städtische Kliniken, Karlsruhe; Department of Radiation Oncology, University of Erlangen, Erlangen; Department of Urology, Krankenhaus am Urban, Berlin; and Department of Urology, University of Mannheim, Mannheim, Germany.

Submitted June 12, 2002; accepted, December 2, 2002.

Address reprint requests to J. Classen, MD, Department of Radiation Oncology, University of Tübingen, Hoppe-Seyler-Str 3, D-72076 Tübingen, Germany; email: johannes.classen@med.uni-tuebingen.de.

0732-183X/03/2106-1101/$20.00

results for the per-protocol population of the study were published previously.[7,8] This article reports final results for the entire study population of the trial, analyzing actuarial 6-year data.

PATIENTS AND METHODS

Patient Selection

Patients with histologically confirmed pure testicular seminoma with clinical stage IIA (retroperitoneal lymph node metastases < 2 cm) or IIB (lymph node metastases 2 to 5 cm) according to the Royal Marsden classification system[6] were considered assessable for the study. High inguinal semicastration was required in every patient. Patients with a history of prior radiotherapy or chemotherapy were excluded. All patients provided written informed consent according to the Declaration of Helsinki.

Staging Requirements

The staging procedure comprised a computed tomography (CT) scan of chest, abdomen, and pelvis, along with pre- and postoperative assessment of alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (βHCG). A bipedal lymphangiogram for evaluation of retroperitoneal lymph nodes was optional. Patients with elevated AFP levels were not admitted to the study. During the first year of the trial, only patients without βHCG elevation were admitted, because it was assumed that βHCG-positive tumors would carry an adverse prognosis. During the second and third year of the trial, however, patients with elevated βHCG levels of up to 200 IU/L were admitted as well, because it had been demonstrated that βHCG elevation does not adversely affect the prognosis of seminoma patients.[9]

Treatment

Radiotherapy was applied through ventro-dorsal opposing fields covering macroscopically enlarged lymph nodes, as assessed by CT with a 2-cm safety margin, together with para-aortic/paracaval and ipsilateral high iliac lymph nodes (hockey-stick portals). The upper border of the field was posed at the cranial rim of the 11th thoracic vertebra, and the lower field margin was set to the cranial rim of the ipsilateral acetabulum (Fig 1). The lateral field margins for the para-aortic region were defined by the ends of the lateral vertebral processes, resulting in a width of the fields between 9 and 11 cm. The lateral borders for the iliac region were defined by a line from the upper rim of the acetabulum to the end of the lateral process of the fourth lumbar vertebra. The para-aortic and iliac regions were treated in one field. Individualized absorbers were used for shaping of the fields. All radiation portals were assigned using treatment simulators. Irradiation was performed with 4- to 20-MV photons of linear accelerators. Both opposing fields were treated every day for 5 days per week with a fraction of 2.0 Gy per day as specified in the International Commission on Radiation Units and Measurements (ICRU) 29 report for opposing fields. A total dose of 30 Gy was applied over 15 days for patients with stage IIA disease. For patients with stage IIB disease, the dose was increased to 36 Gy. A boost treatment was not performed.

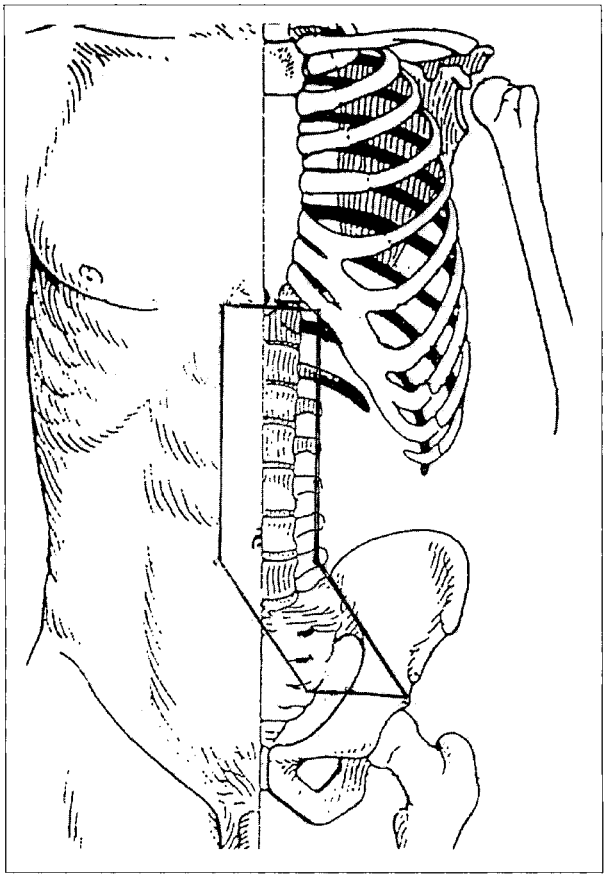

Fig 1. Treatment portals used for treatment of stage IIA and IIB seminoma.

Follow-Up

Follow-up examinations were performed every 3 months for the first 2 years after radiotherapy and every 6 months thereafter. Clinical examination, analysis of AFP and βHCG, chest x-ray, and assessment of late toxicities were required at each visit. Abdominal CT scans were taken twice a year for the first 2 years and annually thereafter. Abdominal ultrasound was performed in turn with abdominal CT scans (twice a year during the first 2 years and once a year after the second year).

Monitoring of Side Effects

Acute and late side effects of radiotherapy (nausea and intestinal and cutaneous side effects) were monitored and recorded according to the European Organization for Research and Treatment of Cancer/World Health Organization scores.

Assessment of Recurrences

Recurrent tumor sites were investigated by CT or magnetic resonance imaging. The CT and magnetic resonance imaging films were compared with the initial simulation films of the individual patient to determine the location of recurrent disease in relation to the radiation portals.

End Points

The primary end point of the study was relapse-free survival at 5 years. Because a potent salvage chemotherapy regimen is available for patients who experience relapse, disease-specific survival was chosen as a secondary end point with an expected survival of at least 95% at 5 years. Furthermore, acute and late gastrointestinal and cutaneous toxicities of treatment (monitored as outlined above) were defined as secondary end points.

Data Management

Data of the primary pathology report, diagnostic work-up, treatment, and follow-up of each patient were recorded on specially prepared forms and entered into a computerized database at the study coordinating center (University of Tübingen, Germany) using the study monitoring system of the Institute for Medical Information Processing. After the database for this final analysis was closed (December 30, 2001), all data were transferred to the Institute for Medical Information Processing for further data processing.

Statistical Methods

The trial was designed as an observational study with a scheduled recruitment period of 3 years, assuming a rate of recruitment of 25 patients per year and an acceptable rate of relapse of no more than 15% for the entire study population. With an expected population of 75 patients, a one-sided 95% confidence interval (CI) for a single proportion using the large sample normal approximation will extend 5.4% from an expected proportion of 9%. Thus a 9% crude relapse rate for the entire study population with a one-sided 95% confidence limit extending to 14.4% would ensure that the highest acceptable relapse rate of 15% would not be surpassed. Treatment failure was continuously monitored over the treatment period, and early termination

Table 1. Distribution of Primary Tumors by T Stage According to 1987 Tumor-Node-Metastasis Classification

Pathologic T Stage	Stage IIA		Stage IIB	
	No. of Patients	%	No. of Patients	%
1	43	65.2	17	81
2	18	27.3	4	19
3	5	7.5	0	0
4	0	0	0	0

of the study was planned once the critical relapse rate was observed during the recruitment period. In the final analysis, relapse rates were calculated from the end of radiotherapy using the Kaplan-Meier method.[10] Continuous variables were described by use of statistical characteristics (means ± SDs). Discrete variables were described as counts and percentages. For statistical analysis, the database was converted into SAS files, and the SAS System (SAS 8.0 for Windows; SAS Institute, Cary, NC) was used.

RESULTS

Between April 1991 and March 1994, 94 patients were enrolled onto the study by 30 participating centers throughout Germany (see Appendix). After the database was closed, 87 patients were assessable for the primary end points, and seven patients were lost to follow-up and were excluded from the final analysis (five patients with stage IIA and two patients with stage IIB seminoma). Median time to follow-up was 70 months (range, 3 to 111 months). There were 66 patients with stage IIA and 21 patients with stage IIB disease. Median age of the patients was 32.5 (range, 21 to 63 years**)** and 32 years (range, 24 to 47 years) for stage IIA and IIB, respectively. A right-sided tumor was observed in 40.2% of the patients, a left-sided malignancy was observed in 59.8%, and there were no bilateral cancers.

Histopathology

Sixty-three patients with stage IIA and 19 patients with stage IIB (94.3%) presented with classical seminoma. Two patients (one with stage IIA and one with stage IIB disease) had a spermatocytic seminoma, and three patients presented with anaplastic seminoma (two with stage IIA and one with stage IIB disease). The distribution by T stage is shown in Table 1.

Protocol Violations

Sixty-one patients (70.1%) were staged and treated strictly per protocol, whereas 26 patients (29.9%) showed protocol deviations in either the staging procedure or the treatment schedule. Protocol violations were classified as major if they had a potentially negative effect on the therapeutic efficacy of irradiation or if they were apt to increase treatment-related toxicities. Protocol violations were classified as minor if no adverse effect on treatment outcome or toxicity of irradiation was assumed. Criteria for classification of protocol violations as either major or minor are listed in Table 2. According to these criteria, 22 patients (25.3%) showed major protocol violations, and four patients (4.6%) showed minor violations.

Treatment

Median doses of radiation were 30 Gy for stage IIA (range, 26 to 36 Gy) and 36 Gy for stage IIB (range, 36 to 37 Gy) disease. In 82 patients, treatment portals were assigned according to protocol requirements, whereas five patients received bilateral iliac treatment. These patients were classified as having major protocol violations.

Table 2. Criteria for Major and Minor Protocol Violations and Number of Patients Affected

	No. of Patients
Criteria for major protocol violations	
No thorax computed tomography and no chest x-ray for staging	1
No abdominal computed tomography for staging	0
No alpha-fetoprotein evaluation for staging	14
Deviation from stage-dependent dose prescription	16
Criteria for minor protocol violations	
Cobalt-60 treatment	5

NOTE. For some patients, more than one criterion applied.

Tumor Control and Survival

Four patients have experienced relapse from treatment. All four patients were staged and treated according to the protocol. Two patients with stage IIA disease experienced treatment failure 33 and 40 months after the end of radiotherapy, respectively. One patient suffered from a mediastinal relapse; the second patient failed with a left-sided field-edge recurrence. Two patients with stage IIB disease experienced relapse 10 and 17 months after the end of radiotherapy, respectively. One of these patients suffered from a mediastinal relapse; the second patient had mediastinal and pulmonary metastases. All four patients were treated with a salvage regimen of platinum-based chemotherapy. Two patients were submitted to resection of residual mediastinal tumor. Currently, all four patients are in continuous complete remission. Six-year disease-free survival for patients with stage IIA disease was 95.3% (95% CI, 88.9% to 100%) for patients with minor or without protocol violations, and 100% for patients with major violations. Because of the small number of stage IIB patients, no separate analysis was performed with respect to the type of protocol violation. Six-year disease-free survival for patients with stage IIB disease was 88.9% (95% CI, 74.4% to 100%) (Fig 2). There were no cases of seminoma-related death. One patient with stage IIB disease committed suicide 92 months after the end of radiotherapy. There was no evidence of disease at the time of death. Disease-specific survival was 100% for stage IIA and IIB disease.

Acute Toxicity

Maximum acute toxicity of radiotherapy was moderate and was dominated by grade 1 nausea, which was observed in 53% and 52% of stage IIA and IIB patients, respectively. No grade 4 side effects were documented (Table 3). There was no significant difference in acute toxicity between stage IIA and IIB disease. Furthermore, in stage IIA disease, no statistically significant differences between patients treated per protocol and patients with major protocol violations were observed.

Late Toxicity

Late grade 1 skin toxicity with mild hyperpigmentation of the skin in the radiation field was found in one patient with stage IIB disease. There was no soft tissue fibrosis or late

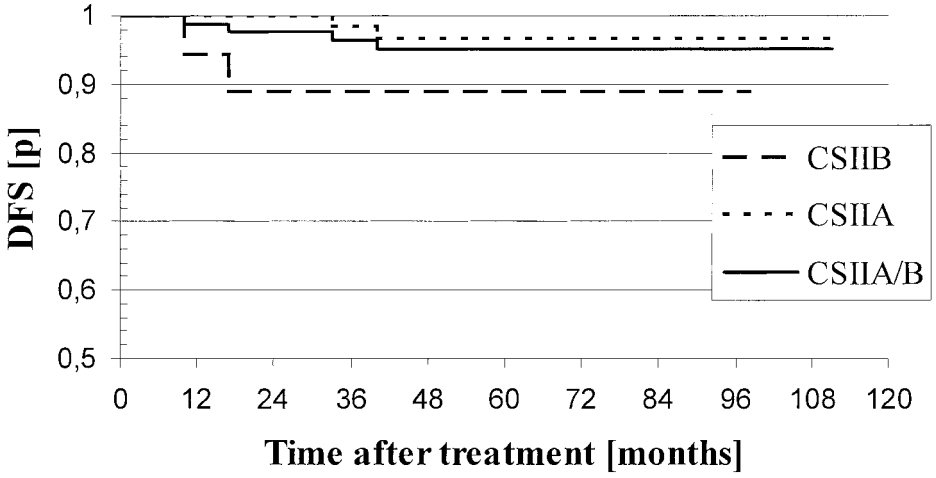

Fig 2. Disease-free survival (Kaplan-Meier curves) for stages IIA and IIB seminoma and the overall population. Abbreviations: DFS, disease-free survival; CS, clinical stage.

Pts. at risk

CSIIA	66	64	61	59	53	42	34	22	14	2	0
CSIIB	21	17	17	16	12	11	10	5	2	0	0

gastrointestinal toxicity. No second malignant tumors have been observed to date.

DISCUSSION

Our study, which to our knowledge is the second prospective trial in stage II radiotherapy,[11] provides further evidence for the excellent prognosis of stage IIA and IIB testicular seminoma. The disease-specific survival rate in our series was 100% because of the availability of highly efficient salvage chemotherapy for those patients who experienced treatment failure after primary radiotherapy. Furthermore, relapse rates of 4.7% and 11.1% for stage IIA and IIB disease, respectively, compare favorably with those of other reports in the literature.[3,11-14] One reason for these comparatively low relapse rates may be the careful staging procedure that was obligatory for all patients. Although in many historic series staging largely was based on clinical and lymphangiographic assessment of abdominal disease, all of our patients underwent abdominal CT for evaluation of the retroperitoneum. Furthermore, mediastinal disease was excluded by thoracic CT in the majority of our patients. Simulator-based treatment planning and delivery of radiation by linear accelerators in the large majority of patients, which provided a favorable dose distribution, may have contributed to the superior results of radiotherapy compared with older series.

Table 3. Maximum Acute Toxicity of Radiotherapy Assessed for Skin, Nausea, and Diarrhea

	Skin (%)		Nausea (%)		Diarrhea (%)	
RTOG/WHO Grade	IIA	IIB	IIA	IIB	IIA	IIB
0	91	76	27	24	70	57
1	9	24	53	52	15	10
2	0	0	12	14	9	24
3	0	0	8	10	6	10
4	0	0	0	0	0	0

Abbreviations: RTOG, Radiation Therapy Oncology Group; WHO, World Health Organization.

In our earlier report,[7] only patients who had been treated with strict adherence to the protocol were analyzed. Our current report summarizes the results of all patients in the sense of an intention-to-treat analysis. Protocol violations concerning either the staging procedure or radiotherapy itself were observed in 27 (31%) of 87 patients in our trial. However, separate analyses of treatment efficacy and acute toxicity of irradiation for patients with major violations as compared with the group treated per protocol or showing minor violations did not disclose any adverse effect on treatment outcome. All patients relapsing from radiotherapy were part of the per-protocol population. Thus treatment failure cannot be attributed to incorrect staging or treatment in any patient.

Toxicity of treatment has been remarkably low in our series. The leading side effects were nausea and diarrhea, which were observed in 10% of stage IIB and 8% and 6% of stage IIA patients, respectively. There was no grade 4 toxicity. Major late side effects have not been observed. In particular, there was no case of peptic ulceration or other gastrointestinal toxicity. Furthermore, no secondary malignancy has been reported so far, although the time of follow-up may be too short to reliably estimate the risk of second cancers in our patients. This profile of favorable toxicity has to be taken into consideration whenever more toxic regimens for primary treatment of stage II seminoma are investigated to improve tumor control probability.

Prophylactic mediastinal irradiation has not been applied in our patients because it is currently considered to be of limited value for tumor control, and it increases the risk of cardiac disease,[1] limits the hematologic reserve for salvage chemotherapy, and possibly increases the risk of secondary malignant tumors.[2] Recently, prophylactic supraclavicular irradiation has been recommended to reduce the risk of relapse in this region.[3] In our series, three patients experienced relapse with involvement of mediastinal lymph nodes. No isolated supraclavicular relapse occurred. Thus prophylactic mediastinal or limited supraclavicular treatment would have been of no use in 96.6% and

100% of our patients, respectively. Our data therefore do not support prophylactic supradiaphragmatic treatment, but rather provide evidence that limitation of the treatment portals to infradiaphragmatic lymph nodes does not compromise treatment outcome for the patients.

All but five patients in our series were treated with a limited-volume hockey-stick field covering only para-aortic and ipsilateral high iliac commune lymphatics. Previous reports for stage II seminoma usually applied more extensive treatment portals that covered the entire ipsilateral iliac and inguinal chain of lymph nodes as well as the contralateral pelvis.[3,12,13,15] Our study was not designed to disclose beneficial effects of reduced treatment portals. However, limitation of the target volume offers the possibility of reducing treatment-related toxicity such as gastrointestinal side effects or radiation scatter to the contralateral testis. Only one of our patients developed a lateral para-aortic field edge relapse; there was no pelvic or inguinal recurrence. Our study provides evidence that the portal definition for limited-volume hockey-stick irradiation is sufficient for safe tumor control and might further reduce treatment-related toxicities compared with historic series.

Median doses of 30 and 36 Gy applied in our study for stage IIA and IIB groups, respectively, yielded 100% in-field tumor control and compared favorably with total doses of previous reports in the literature.[3,11,12,15] The lowest dose applied in our series was 26 Gy in three stage IIA patients. Excellent tumor control of stage IIA and IIB disease with low total doses in the range of 25 to 30 Gy has also been reported by others.[3,12] Judging from these data, there seems to be potential for an additional dose reduction in patients with stage II seminoma, even though a clear dose-response relationship has not yet been established.

Because of the high relapse rates of up to 33% reported for stage IIB seminoma,[11] the role of radiotherapy in stage II has repeatedly been questioned. However, data for primary chemotherapy are limited. A relapse rate of 9% has been reported for a modified etoposide and cisplatin (EP) schedule in stage IIA/B seminoma at a 33% risk of grade 3/4 leukopenia.[16] This relapse rate compares well with tumor control rates after radiotherapy for combined stages IIA/B in the range of 4% to 5% as observed in our trial and reported by others.[14,17] Hence, modified EP obviously lacks superiority over modern standard radiotherapy both with respect to tumor control and treatment-related toxicity. It may be expected that conventional EP or cisplatin, etoposide, bleomycin chemotherapy will cure stage IIA and IIB seminoma in virtually all patients. However, intensified systemic treatment will further increase acute and potential late toxicities with etoposide-associated leukemia at doses greater than 2 g/m^2.[18] Carboplatin, which has proven activity in early- and advanced-stage seminoma,[19,20] has been investigated for stages IIA/B seminoma in a prospective trial conducted by the German Testicular Cancer Study Group. The reported rate of treatment failure was 15%.[21] Thus carboplatin provides no advantage with respect to tumor control in stages IIA/B seminoma over modern radiotherapy.

Another possible approach for treatment of stage II disease is sequential chemoradiotherapy, which combines potential advantages of both treatment modalities: control of gross metastatic disease by radiation, and eradication of microscopic disease outside the treatment portals by chemotherapy. When one to two courses of carboplatin single-agent chemotherapy were applied followed by infradiaphragmatic radiotherapy, a relapse rate of 7.1% for stage IIA and 5.3% for stage IIB patients has been observed.[13] Compared with historic controls, these figures suggest a considerable improvement in tumor control. However, in the view of modern radiotherapy series, these data must be interpreted with caution, and larger patient series are required to further evaluate the concept of sequential chemoradiotherapy with carboplatin in stage II seminoma.[22]

If the therapeutic index of irradiation as documented in our series is considered in the light of the available treatment alternatives, radiotherapy remains in our opinion the first treatment choice for these patients. It offers excellent treatment outcome with respect to tumor control, disease-specific survival, and treatment-related toxicity.

APPENDIX

The appendix is available online at www.jco.org.

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