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CLINICAL INVESTIGATION

Patterns of Disease Progression and Outcome of Patients With Testicular Seminoma Who Relapse After Adjuvant or Curative Radiation Therapy

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Purpose: Radiation therapy is a possible treatment strategy for patients with testicular seminoma after orchiectomy in clinical stage I or II disease. Little is known about the outcome of patients who experience a relapse after radiation therapy.

Methods and Materials: Data from 61 patients who relapsed after adjuvant or curative radiation therapy from 17 centers in 11 countries were collected and retrospectively analyzed. Primary outcomes were disease-free and overall survival. Secondary outcomes were time to relapse, stage at relapse, treatment for relapse, and rate of febrile neutropenia during chemotherapy for relapse.

Results: With a median follow-up of 9.9 years (95% confidence interval [CI], 7.5-10.9), we found a 5-year disease-free survival of 90% (95% CI, 79-95) and a 5-year overall survival of 98% (95% CI, 89-100). Sixty-six percent of patients had stage III disease at time of relapse and 93% of patients fell into the good prognosis group per the International Germ Cell Cancer Collaborative Group classification. The median time to relapse after radiation therapy was 15.6 months (95% CI, 12-23). Twenty-two (36%) patients relapsed more than 2 years after radiation therapy and 7 (11.5%) patients relapsed more than 5 years after radiation therapy. One-third of relapses was detected owing to patients' symptoms, whereas two-thirds of relapses were detected during routine follow-up. The majority (93%) of cases were treated with cisplatin-based chemotherapy. The rate of febrile neutropenia during chemotherapy was 35%. Five patients experienced a second relapse. At last follow-up, 55 patients (90%) were alive without disease. Only 1 patient died owing to disease progression.

Conclusions: Cisplatin-based chemotherapy for patients with seminoma who have relapsed after treatment with radiation therapy alone leads to excellent outcomes. Patients and physicians should be aware of possible late relapses after radiation therapy.

Introduction

Approximately 50% to 60% of patients with testicular cancer present with pure seminoma, and three-fourths of them have clinical stage I (CS I) disease.[1,2] Clinical stage II (CS II) disease is found in 15% to 20% of all patients with seminomatous germ cell tumors (SGCT).[3,4] During the past decades, a histologic shift with an increase in SGCT and an increase in patients' ages has been observed.[1,5] For CS I, 3 different management strategies—active surveillance, adjuvant para-aortic irradiation, and adjuvant chemotherapy with 1 cycle of carboplatin—have been offered to patients with SGCT after orchiectomy. Contemporary guidelines recommend active surveillance as the preferred option for CS I owing to potential harm of adjuvant strategies. This has limited the role of adjuvant radiation therapy for selected cases that are not suitable for active surveillance or adjuvant carboplatin.[6-9] For patients with retroperitoneal lymph node metastases, treatment options include curative radiation therapy for CS IIA disease and for nonbulky (≤3 cm) CS IIB disease or curative chemotherapy with 3 cycles of cisplatin, etoposide, and bleomycin or 4 cycles of cisplatin and etoposide.[6-8,10] The 5-year risk of relapse after radiation therapy lies between 3% and 4% for CS I and is up to 24% for CS II.[3,11-14] Some small retrospective studies have described patterns of relapse after radiation therapy in SGCT, but whether the outcome of patients is compromised by the previous delivery of radiation therapy is unclear.[3] We therefore retrospectively collected data from 17 centers worldwide to analyze patterns of relapse, mode of detection, and salvage treatment approaches. We also collected data regarding febrile neutropenia (FN) during subsequent chemotherapy, given that we previously reported para-aortic radiation therapy as a risk factor for FN in this setting.[15]

Methods and Materials

We contacted centers worldwide, mostly through the network of the International Germ Cell Cancer Collaborative Group (IGCCCG), and we explored the group's interest in contributing data from patients with SGCT who presented with a relapse after adjuvant or curative radiation therapy for former CSI or CSII disease. After identification of suitable cases, detailed information on patients was collected through predefined structured questionnaires. Approval from local ethics committees were obtained. Information was collected on patient characteristics at the time of primary radiation therapy treatment, and time to, detection of, and location of relapse. Data on imaging modalities, elevation of tumor markers at time of relapse, and treatment of relapse (surgery, radiation therapy, chemotherapy, or combination) as well as outcome of this treatment were gathered. If applicable, data regarding further relapses and treatment modalities of subsequent relapses were obtained as well as the cause of death. Data were collected and anonymized locally and subsequently transferred and entered into a joint database in Graz, Austria. The study was approved by the institutional review board of the Medical University of Graz, Austria (No. 32-378 ex 19/20).

Patients

Comprehensive data of SGCT patients who had received adjuvant or curative treatment with radiation therapy for CS I or II disease and who had experienced a relapse were retrospectively collected within a multi-institutional and multinational effort. Inclusion criteria were male sex, age 18 years and older, pure SGCT as initial histology, CS I or II disease, and normal alpha-fetoprotein value at initial

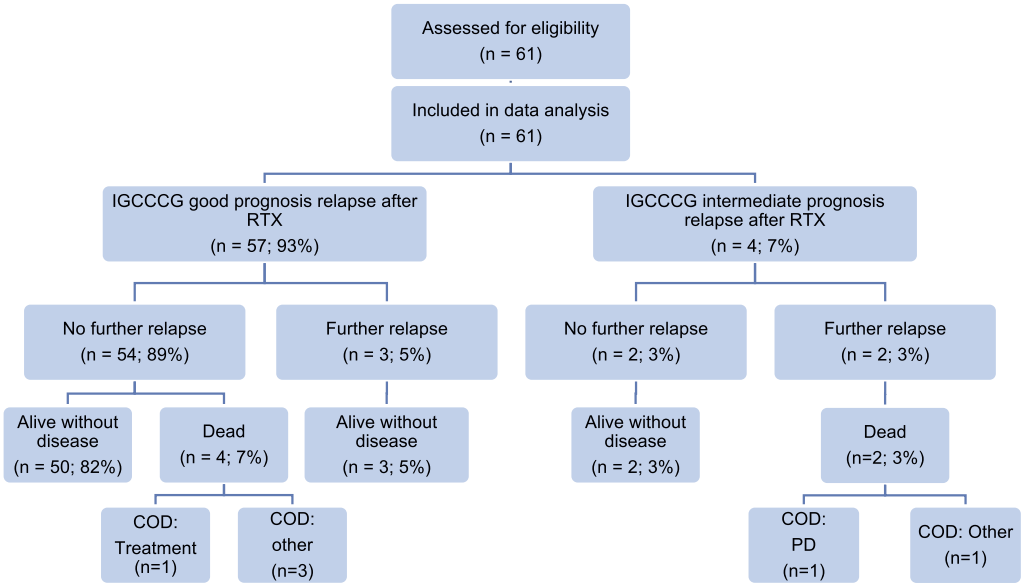

Fig. 1. Overview of patients. *Abbreviations*: COD = cause of death; IGCCCG = International Germ Cell Cancer Collaborative Group; PD = progressive disease; RTX = radiation therapy.

diagnosis. Further inclusion criteria were orchiectomy for SGCT, delivery of adjuvant or curative radiation therapy, and clinical or radiologic confirmation of recurrent SGCT. Exclusion criteria were nonseminomatous histology or any other histology apart from pure seminoma at initial diagnosis. Disease stage was reported according to the International Union Against Cancer classification, and for allocation to prognostic categories the IGCCCG prognostic classification was used.[16-18]

Statistical analysis

Coprimary endpoints were overall survival (OS) and disease-free survival (DFS) calculated from the date of post −radiation therapy relapse. Secondary outcomes were time to relapse, stage at relapse, DFS from initial radiation therapy to relapse, management strategies chosen, rates of subsequent relapses, and frequency of FN. Time to event endpoints other than incidence of relapse were analyzed with the Kaplan-Meier method. Relapse estimates were computed with competing risk cumulative incidence estimators, treating death-from-any-cause as the competing event of interest. Calculation of time to first relapse started with the last date of radiation. The date of radiation was missing in 12 patients. For these patients the start date of radiation was assumed to be 44 days after surgery (median time between date of orchiectomy and start of radiation therapy in patients with both dates available), and the last day of radiation was estimated depending on the applied dose of radiation therapy. Calculation of time to second relapse started with the day of diagnosis of first relapse. Logistic regression models were employed to investigate potential risk factors for FN during chemotherapy for first relapse. All statistical analyses were performed with Stata (Windows version 15, StataCorp, Houston, TX).

Results

Sixty-one patients with SGCT who underwent adjuvant or curative radiation therapy for CS I or CS II between December 1988 and January 2019 at 17 centers from 11 countries and had subsequently developed relapses were included (Fig. 1). All patients (100%) had previously undergone orchiectomy, and median time from orchiectomy to radiation therapy was 44 days (95% confidence interval [CI], 43-58].

Analysis from time of initial radiation therapy in adjuvant or curative intent

Thirty-six (61%), 17 (29%), and 6 (10%) patients had CS I, IIA, and IIB disease, respectively. Among the 23 patients with CS II disease (ie, radiation therapy with curative intent), 18 (78%) patients had CS II at diagnosis, whereas 5 patients (22%) had metachronous relapses after active surveillance. Patients with CS I, IIA, and IIB received a median total radiation dose of 25 Gy (95% CI, 23-27), 32 Gy (95% CI, 30-35), and 36 Gy (95% CI, 31-37), respectively. Among 22 of the 23 CS II patients assessable for response, radiation therapy response categories were complete remission (CR), tumor-marker negative partial remission (PRm−), and progressive disease (PD) in 16 (73%), 3 (14%), and 3 (14%) cases, respectively. Two of the 3 patients who did not respond to radiation therapy had distant metastases on the next scan. The third patient had a locoregional relapse.

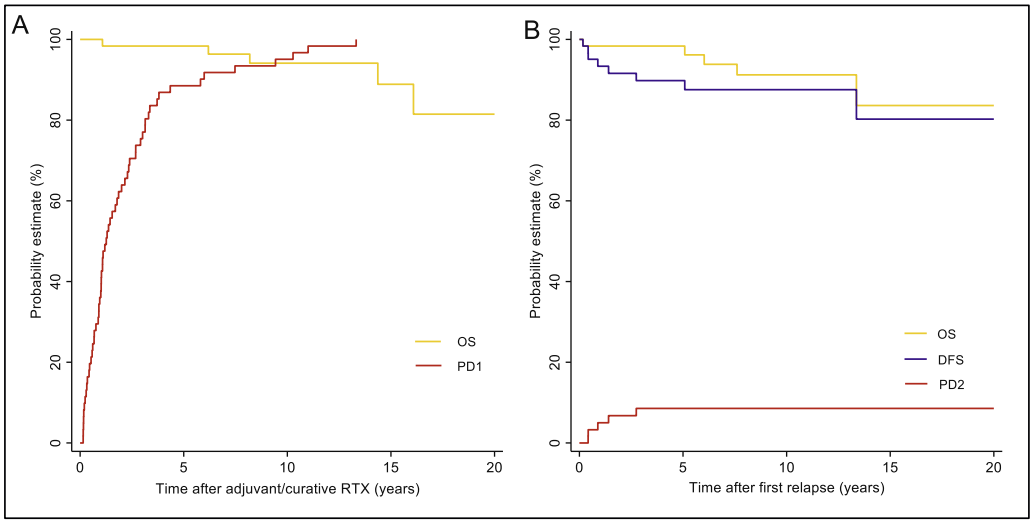

Fig. 2. (A) Overall survival (OS) and rate of recurrence (progressive disease 1 [PD1]) after adjuvant and/or curative radiation therapy (RTX) in the whole study population. (B) OS and disease-free survival (DFS) from the date of relapse post−radiation therapy and the rate of subsequent relapse (progressive disease 2 [PD2]).

After the last day of radiation therapy, median follow-up for our cohort was 11.7 years, with 75% and 25% of the cohort having been followed for at least 6.9 and 15.9 years. During this interval, median time to first relapse was 15.6 months (95% CI, 12-23) with 25% and 75% of all relapses having occurred within 0.7 and 2.9 years (Fig. 2A). However, 22 (36%) of the 61 patients relapsed more than 2 years after radiation therapy and 7 (11.5%) patients relapsed more than 5 years after radiation therapy. The 5-, 10-, and 20-year OS estimates were 98% (95% CI, 89-100), 94% (83-98), and 81% (56-93), respectively (Fig. 2A).

Analysis from time of first relapse

The median age of patients at the time of relapse was 41 years, and all patients had performance status (PS) 0 or 1 (Table 1). Approximately one-third of relapses were detected owing to patients becoming symptomatic outside routine follow-up. Symptoms varied depending on the site of relapses (eg, palpable enlarged lymph nodes, dysphagia in a patient with a big mediastinal relapse, and abdominal pain in patients with bulky retroperitoneal disease). In 5 patients elevated tumor markers (lactate dehydrogenase or human chorionic gonadotropin) led to further investigations. Among the different diagnostic modalities for relapse detection, more than half of first relapses were detected by imaging (Fig. E1). Sixty-six percent of patients had CS III at the time of relapse, primarily affecting lymph nodes outside the target area of the previous radiation therapy (Table 1). Notably, only 4 relapses (7%) affected more than 1 organ system, and only 4 relapses (7%) were classified as IGCCCG "intermediate risk" (Table 1).

Relapses were almost exclusively managed with chemotherapy (n = 57, 93%), with bleomycin (BEP) being the most frequent chemotherapy regimen (n = 40, 70%) (Fig. 3). Outcomes of treatment for first relapse were CR (n = 44, 72%), PRm− (n = 15, 25%), PRm+ (n = 1, 2%), and unclear (n = 1, 2%). Three patients with PR went on to have surgery for residual masses of which 1 specimen contained residual vital cancer cells.

After a median follow-up of 9.9 years after diagnosis of first relapse, we observed 5 second relapses (8%) and 6 patients (10%) died (Fig. 2B). Accounting for death from any cause as a competing risk, this corresponded to a cumulative 1-, 3-, 5-, 10-, and 20-year incidence of progression after a first relapse of 5%, 9%, 9%, 9%, and 9%, respectively. Second relapses were managed exclusively with chemotherapy, including BEP (n = 1), high-dose chemotherapy (n = 2), and other salvage regimens (n = 2). Outcomes of these treatments were CR (n = 2, 40%), PRm− (n = 2, 40%), and stable disease (n = 1, 20%).

The 6 deaths were attributed to tumor progression (n = 1), acute treatment-related complications (n = 1), and other causes (n = 4). The 1 treatment-related death was a 68-year-old patient who had an ischemic stroke during cisplatin and etoposide chemotherapy. The 5-, 10-, and 20-year OS estimates were 98%, 91%, and 84% with corresponding DFS estimates of 90%, 88%, and 80%, respectively (Fig. 2B). There was no significant difference in DFS and OS when comparing patients who had received radiation therapy for CS I or CS II (Fig. 4; log-rank $P = .874$ and $P = .628$ for DFS and OS, respectively). For the subset of patients with late relapses after 5 years or more, the 5-year DFS rate was 100% and the 5-year OS rate was 100%.

Exploratory analysis: FN due to chemotherapy for first relapse

Fifty-seven (93%) of the relapses were treated with chemotherapy. Twenty (35%) of these 57 patients developed at

Table 1 Characteristics at relapse

Variable	n (% missing)	Summary estimate
Age (y)	60 (2%)	41 [39-44]*
ECOG performance status	52 (15%)	-
0 points	-	44 (85%)
1 point	-	8 (15%)
Detection of relapse	60 (2%)	-
Within routine follow-up	-	40 (67%)
Triggered by symptoms	-	20 (33%)
Tumor localization at relapse	61 (0%)	-
Lymph nodes: retroperitoneal		13 (21%)
Lymph nodes: iliac/pelvic		8 (13%)
Lymph nodes: mediastinal	-	14 (23%)
Lymph nodes: other nonregional	-	13 (21%)
Lung	-	5 (8%)
Bone	-	2 (3%)
Other location	-	2 (3%)
Multiple locations	-	4 (7%)
Clinical stage at relapse	61 (0%)	-
IIB	-	14 (23%)
IIC	-	7 (11%)
III	-	40 (66%)
Prognosis group at relapse	60 (2%)	-
IGCCCG "good risk"	-	57 (93%)
IGCCCG "intermediate risk"	-	4 (7%)
Treatment of relapse		-
Chemotherapy		48 (79%)
BEP	-	40 (70%)
EP	-	14 (25%)
VIP		2 (4%)
Other regimen		1 (2%)
Chemotherapy + surgery		3 (5%)
Chemotherapy + radiation therapy		6 (10%)
Radiation therapy	-	3 (5%)
Surgery	-	1 (2%)
Number of chemotherapy cycles	57 (0%)	3 [3-4]*

Abbreviations: BEP = bleomycin, etoposide, and cisplatin; ECOG = Eastern Cooperative Oncology Group; EP = etoposide and cisplatin; IGCCCG = International Germ Cell Cancer Collaborative Group; IQR = interquartile range; VIP = etoposide, ifosfamide, and cisplatin.
* Data are expressed as median [IQR].

least 1 episode of FN. Twenty-three patients (40%) received primary prophylaxis with granulocyte colony-stimulating factor (G-CSF). Nine (40%) of them had FN despite G-CSF prophylaxis. The rate of FN in patients not receiving primary G-CSF was 32%. The risk of FN was higher in patients ≥40 years of age (n = 34) versus patients below this age cutoff (n = 27) (47% vs 19%, χ^2 $P = .031$). The cutoff at 40 years was based on previous publications suggesting higher rates of side effects in patients with germ cell tumors older than 40 years.[19] Otherwise, we did not observe associations between Eastern Cooperative Oncology Group performance status, primary use of G-CSF, blood counts before chemotherapy, total radiation dose, radiation field and stage at relapse and the risk of FN (Table E1).

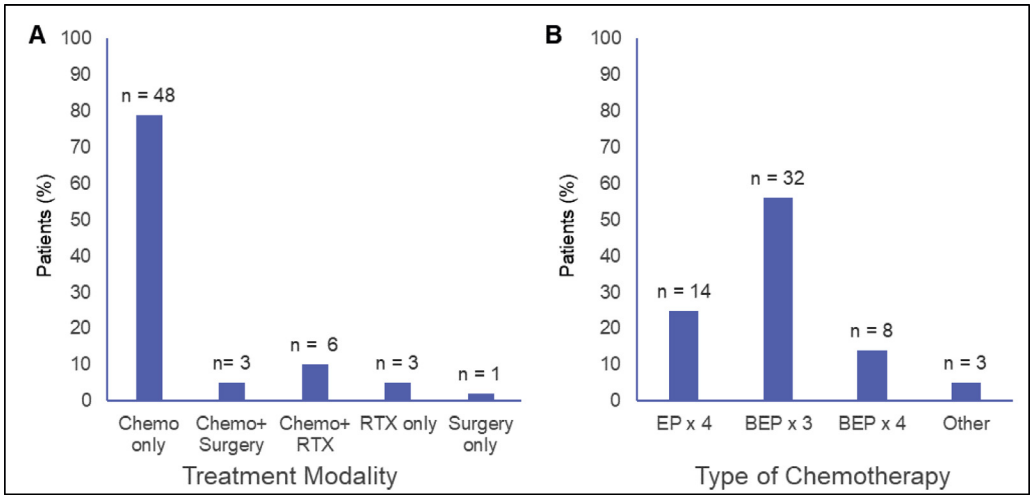

Fig. 3. Treatment of relapse after radiation therapy. (A) Treatment modality used. (B) Type of chemotherapy chosen for patients. *Abbreviations*: BEP = bleomycin, etoposide, and cisplatin; EP = etoposide and cisplatin; RTX = radiation therapy.

Exploratory analysis: second primary malignancies

Five patients (8%) developed a second primary malignancy (SPM) during follow-up. One other patient developed a second primary testicular cancer and was not included in this analysis. The SPMs occurred exclusively after patients had received chemotherapy. The median time between the last day of radiation therapy and the occurrence of the second malignancy was 7 years (95% CI, 2.5-13). Among the 5 SPMs, there were 3 hematological malignancies (2 acute leukemia, 1 chronic leukemia), 1 renal cell cancer and 1 colorectal cancer, and 3 of the 5 patients (60%) died of their SPM (median OS after diagnosis of SPM: 3.6 years).

In modeling SPM as a time-dependent variable, the occurrence of SPM was associated with a 58-fold increase in the risk of death (transition hazard ratio, 57.8; 95% CI, 5.7-593.5; $P = .001$), and this association prevailed after adjustment for age (adjusted transition hazard ratio, 43.6; 95% CI, 4.0-475.1; $P = .002$).

Discussion

This retrospective analysis showed that patients with SGCT and a relapse after radiation therapy for CS I and CS II disease have an excellent outcome. With a median follow-up of 9.9 years, we found a 5-year DFS rate of 90% and a 5-year OS rate of 98%. Only 1 patient died owing to disease progression.

Sixty-six percent of patients had CS III disease at the time of relapse, primarily affecting lymph nodes outside the target area of the previous radiation therapy. This includes 2 of the 3 patients who did not respond to radiation therapy and showed progressive disease on the next scan. Presumably, these patients were harboring occult micrometastases in

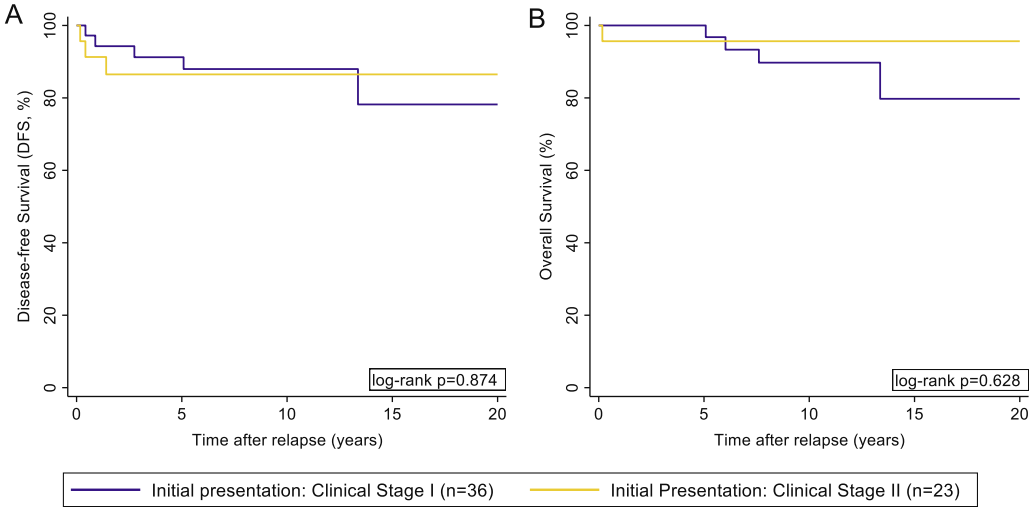

Fig. 4. (A) Disease-free survival according to clinical stage of initial presentation before the application of radiation therapy. (B) Overall survival according to clinical stage of initial presentation before the application of radiation therapy.

distant lymph nodes at the time of radiation therapy. They were cured with subsequent chemotherapy. Thirty-four percent of patients (n = 21) relapsed in retroperitoneal or pelvic lymph nodes. All of them responded to subsequent treatment. Only 1 of them had a second relapse but achieved a CR with subsequent chemotherapy.

When comparing the relapse pattern of patients with initial CS I of our cohort with patients who received adjuvant chemotherapy with carboplatin from the retrospective study by Fischer et al,[20] only 15% of patients relapsed with CS III and 84% with CS II after having received adjuvant carboplatin, whereas in our cohort 64% of patients presented with CS III and 36% with CS II disease.[20]

Our analysis shows that radiation therapy seems not to affect chemosensitivity of SGCT and that patients with a relapse after radiation therapy have similar outcomes as patients with de novo metastatic disease. In the updated IGCCCG classification published in 2021, the 5-year PFS rate was 89% (95% CI, 87%-90%) and the 5-year OS rate was 95% (95% CI, 94%-96%) in good prognosis patients, and 79% (95% CI, 70%-85%) and 88% (95% CI, 80%-93%) in intermediate prognosis patients, respectively.[17] This is comparable to the 5-year DFS of 90% and the 5-year OS of 98% observed in our cohort of patients with SGCT who relapsed after radiation therapy. The median time to relapse was 15.6 months. However, 7 relapses (11.5%) were detected more than 5 years after the last day of radiation. Four of these late relapses were histologically confirmed and 4 patients were symptomatic from their disease at the time of relapse. All these patients were classified as good prognosis and were without evidence of disease at last follow-up after chemotherapy.

Another finding of our analysis is the observed high rate of FN during chemotherapy for relapsed disease after radiation therapy. The reported FN rate during etoposide and cisplatin (EP) or BEP chemotherapy for primary metastatic disease is 10% to 20%, and the decision on whether to prescribe primary G−CSF support should be evaluated by an individual assessment of FN risk factors for each patient.[21] We found a 35% risk of FN in patients undergoing curative chemotherapy for disease relapse after radiation therapy. The ability of the bone marrow compartment to recover and regenerate is dependent on the volume of bone marrow within the irradiated field. Radiation therapy to para-aortal lymph nodes involves around 25% of bone marrow.[15,22,23] An association between prior radiation therapy and a higher FN risk is therefore highly plausible.

Until 1 decade ago, radiation therapy was considered a valid adjuvant treatment option for patients with CS I seminoma because of its high radiosensitivity and predictable pattern of spread to the para-aortic lymph nodes. Based on the assumed higher risk of secondary malignancies its use has decreased significantly and is currently discussed controversially.[9,24-28] However, this observed higher risk of secondary malignancies must be viewed critically, as radiation dose, treatment volume and technique have improved remarkably since publication of the above cited studies.[14,26] Treatment field and dose reduction, and improvements in dose planning have demonstrated to significantly reduce the incidence of secondary malignancies.[29-31] Because the TE18 trial showed the noninferiority of 20 Gy compared with 30 Gy, the recommended radiation dose for CS I is now 20 Gy in 10 fractions applied in a para-aortic strip field. For CS II, the recommended doses are 30 Gy for CS IIA disease and 36 Gy for CS IIB, including the retroperitoneal and proximal ipsilateral iliac lymph nodes.[14,30] In our analysis, 5 patients developed secondary malignancies. One patient died of metastatic colorectal cancer which he developed 9 years after radiation therapy treatment. Another patient developed kidney cancer 8 years after RT but is still alive without disease. Two patients died owing to leukemia (1 acute myeloid leukemia, 1 chronic lymphatic leukemia), which they developed 8 and 3 years after chemotherapy treatment for the relapse of testicular cancer. The guidelines of the European Association of Urology, the Comprehensive Cancer Network, and the European Society for Medical Oncology recommend active surveillance as the preferred option for CS I seminoma after orchiectomy owing to potential harm of adjuvant strategies.[6-8] All 3 guidelines recommend RT as a treatment option for CS IIA and nonbulky CS IIB. Considering the excellent survival results of patients with CS I seminoma managed with active surveillance, and weighing risks and benefits of adjuvant radiation therapy, surveillance can be seen as the preferred treatment choice for CS I seminoma. For CS II seminoma, the use of radiation therapy can be an attractive alternative to cisplatin-based polychemotherapy, especially for older patients with comorbidities.[32-36] A novel concept comprises the application of carboplatin before radiation therapy to further reduce the recurrence risk and to permit a smaller radiation field.[37] This concept is currently under investigation in the SAKK 01/10 trial (ClinicalTrials.gov identifier: NCT01593241) and a similar concept is being investigated in the SAKK 01/18 trial (ClinicalTrials.gov identifier: NCT03937843). The SEMS and PRIMETEST trial explore an alternative concept with surgery for early metastatic seminoma (ClinicalTrials.gov identifier: NCT02537548) to avoid long-term toxic effects caused by radiation therapy or chemotherapy. There are also risk-adapted chemotherapy trials under investigation. The phase 2 SEMITEP trial investigated a de-escalating treatment approach based on a negative fluorodeoxyglucose positron emission tomography (PET) scan after 2 cycles of EP chemotherapy in low-volume metastatic seminoma (ClinicalTrials.gov identifier: NCT01887340). If patients had a negative PET scan after 2 cycles of EP, patients received only 1 cycle of carboplatin (area under the curve = 7), whereas patients with a persistent positive PET scan proceeded with 2 additional EP cycles. Two-year PFS rates were 93.7% in the carboplatin group and 92.9% in the EP group.[38,39]

Conclusions

According to the present retrospective study, radiation therapy does not seem to affect chemosensitivity of SGCT and patients with a subsequent relapse still have an excellent

outcome. However, the observed substantial rate of late relapses demands attention, especially because most centers finish follow-up for patients with germ cell tumors after 5 years. Physicians should also be aware of an increased rate of FN during chemotherapy after prior radiation treatment.

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