Very Early Relapse (< 1 year) in de novo Metastatic Seminoma is Associated With Reduced Overall Survival

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Abstract

Characteristics and outcome associated with relapse in seminomatous testicular germ cell tumors (STGCT) are still unclear. We aim at evaluating the differences between very early relapse (VER, tumour recurrence < 12 months after successful treatment) and later relapse (LR) in a cohort of 459 patients with STGCT. 20 % of all seminoma relapsed. In the initial metastatic stage, VER was associated with a higher metastatic burden at diagnosis compared to LR, leading to a reduced overall survival in VER.

Introduction: As the characteristics and outcome associated with relapse in seminomatous testicular germ cell tumors (STGCT) are still unclear, this study aims at evaluating the differences between very early relapse (VER) and later relapse (LR) in this cohort of patients. **Material and methods:** This retrospective analysis included 459 patients with STGCT treated from 2000 to 2024, analysing patient characteristics with nonparametric statistics as well as follow-up using Kaplan Meier analyses. VER was defined as tumour recurrence < 12 months after successful treatment. **Results and limitations:** About 94 (20%) patients relapsed during a median follow-up of 19 months [IQR 2-68]. De novo metastatic patients with VER ($n = 38$, 40%) showed a significantly higher number of clinical stages 2C-3 disease (21% vs. 4%, $P = .007$), M-stage ($P = .009$) at diagnosis as well as a higher HCG level ($P = .030$) and LDH levels ($P < .001$; >2x ULN $P = .039$) at start of chemotherapy compared to patients with LR ($n = 56$; 60%). Initial treatment did not significantly differ between VER and LR ($P = .199$). VER after initial metastatic disease was associated with a significantly reduced overall survival compared to LR ($P = .046$), however not after de novo stage I. Our study is limited by its retrospective design. **Conclusion:** Relapse in seminoma occurred in 20% of all patients. In the initial metastatic stage, VER was associated with a higher metastatic burden at diagnosis compared to LR, leading to a reduced overall survival in VER. Consequently, treating physicians should be aware of these patients portending a worse prognosis, potentially discussing an early intensification of systemic treatment.

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Keywords: Germ cell tumor, Overall survival, Seminoma, Testicular cancer, Systemic treatment

Introduction

Testicular germ cell tumors (TGCT) embody the most common solid malignancy in young men between the ages of 20 and 40 years.[1] Due to efficient treatment options including platinum-based chemotherapy, high cures rates can be achieved, irrespective of the postorchiectomy strategy employed.[1,2] Despite these modern treatment options, 15% of clinical stage I seminoma patients have subclinical metastatic disease and will relapse after orchiectomy alone, while 10% to 50% of patients with metastatic TGCT relapse, which needs further multimodality treatment.[1] In the metastatic state, relapse and survival rates depend on the IGCCCG risk classification, as approximately 11% of patients with a good prognosis and 21% with an intermediate prognosis progress from the TGCT

Abbreviations: IGCCCG, International Germ Cell Cancer Collaborative Group; IQR, interquartile range; PC-RPLND, postchemotherapy retroperitoneal lymphadenectomy; RFS, relapse-free survival; STGCT, seminomatous testicular germ cell tumors; TGCT, testicular germ cell tumors.

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within 5 years.[3-5] Here, most seminoma patients relapse within the first 1 to 2 years after initial treatment.[1]

As the characteristics and outcome associated with relapse in seminomatous testicular germ cell tumors (STGCT) are still unclear, this study aims at evaluating the differences between very early (< 1 year after completion of the primary treatment) and later relapse (> 1 year after completion of the primary treatment) in this cohort of patients. Accordingly, the primary aim of this analysis was to evaluate the incidence and clinical outcome for early and later relapse in a large cohort of STGCT patients. The secondary aim was to assess differences in risk factors in patients with very early relapse and later relapse, in the cohort of de novo stage I and metastatic patients.

Patients and Methods

Study Population

The TGCT database at the University Hospital of Cologne was retrospectively analyzed as an observational cohort study. 459 patients with seminomatous TGCT (ICD-10 code C62), which were treated in or referred to our department from 2000 to 2024, are included in the study. Data on age, histology, clinical stage, IGCCCG risk classification, type and duration of treatment as well as follow-up analyses were evaluated. We excluded nonseminoma patients from this study as well as patients with missing data including missing clinical stage, IGCCCG risk classification and follow-up data ($n = 52$). Our study complies with the Declaration of Helsinki and local ethics committee approval was obtained (21-1108). Very early relapse was defined as tumour recurrence < 12 months after successful treatment.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY). We presented continuous variables as median (25th-75th percentile) and categorical variables as *n* (%). Mann-Whitney U test was used for a pairwise comparisons of continuous variables and Pearson's chi-squared test for categorical variables. Relapse-free survival and overall survival were evaluated using the Kaplan-Maier method and compared using the log-rank test. All reported p-values are 2-sided, and *P*-values < .05 were considered statistically significant.

Results

Description of Study Population

Of the eligible 459 patients with seminomatous TGCT, 94 (20%) patients relapsed during a median follow-up of 19 months [IQR 2-68] (Table 2). Of these, 322 (70%) had de novo clinical stage I showing a relapse rate of 20%, and 137 (30%) clinical stage II to III (Table 2). In clinical stage I, 22 (34%) patients had a very early relapse (< 1 year after completion of the primary treatment) and 43 (66%) patients a relapse > 1 year after completion of the primary treatment (Table 2). In de novo metastatic disease, 16 (55%) patients had a very early relapse and 13 (45%) patients a later relapse (Table 2). Taken together, very early relapse occurred more often in the de novo metastatic stage compared to clinical stage I (34% vs. 55%; $P = .052$). The predominant site of relapse in the whole study population was the retroperitoneum (79%, Table 2). The site of relapse (retroperitoneum (R) vs. extra-retroperitoneal (ER)) was not statistically different regarding clinical stage (CS I: 80% [R]/20% [ER] vs. CS II-III [67% {R}/33% {ER}]; $P = .202$) or pretreatment (adjuvant Carboplatin 86% [R]/14% [ER] vs. Cisplatin-based chemotherapy as systemic treatment 78% [R]/22% [ER], $P = .568$). Baseline characteristics and initial treatment of study population are displayed in Table 1.

Clinical Stage, IGCCCG Risk Classification and Risk Factors for Relapse

We next evaluated the clinical stage as well as prognostic group according to the IGCCCG risk classification system of patients as well as potential risk factors for very early and later relapse (Tables 2 and 3).

In the subgroup of patients with de novo metastatic disease, we found that patients with very early relapse showed a significantly higher number of clinical stage 2C-3 disease at the time of orchiectomy (21% vs. 4%, $P = .007$, Table 3) as well as M-stage ($P = .009$, Table 3) compared to patients with later relapse. Furthermore, initially metastatic patients with very early relapse had significantly higher HCG levels ($P = .030$) and LDH levels ($P < .001$) at start of chemotherapy compared to patients with later relapse (Table 3). The biomarker LDH > 2,5 ULN at start of chemotherapy was significantly higher in very early relapsing patients (70% vs. 16%, $P = .039$, Table 3).[5] We did not identify any risk factor for very early relapse in clinical stage 1 (Table 2).

Description of Relapse

Both groups did not show any difference for the development of relapse regarding initial treatment, eg, between surveillance or adjuvant carboplatin in clinical stage 1 ($P = .860$, Table 2) as well as primary RPLND (pRPLND) in the de novo metastatic setting ($P = .199$, Table 3). Adjuvant chemotherapy after pRPLND ($n = 5/23$; 22%) did not show any influence on relapse ($P = .862$) or very early relapse ($P = .505$). Relapse was most commonly treated with salvage chemotherapy (62% or 48%), followed by primary retroperitoneal lymph node resection (pRPLND) (30% or 26%) in patients with de novo stage I or II-III, respectively (Tables 4 and 5). About 1/7 (14%) of the de novo metastatic patients, being treated with pRPLND for relapse, received adjuvant chemotherapy after pRPLND. Regarding treatment burden for relapse therapy in our cohort of patients, we did not find any significant differences regarding the use of induction chemotherapy, postchemotherapy RPLND or primary RPLND between very early relapsing or later relapsing patients or predicting factors for a more intensified treatment of relapse ($P = .757$). Patients with very early after de novo clinical stage II-III showed a higher number of second or third relapses compared to later relapsing patients ($P = .045$, Table 5).

Relapse and Overall Survival

In the Kaplan-Meier estimates, very early relapse after de novo clinical stage II-III was associated with a significantly reduced overall survival (OS) compared to later relapse ($P = .046$, Figure 1), however median overall survival was not reached. In the de novo metastatic patients, 3 (10%) of all patients with very early relapse and no patient with later relapse deceased during follow-up. Relaps-

Table 1 Baseline characteristics and initial treatment of study population (*n = 459*).

Patient characteristics	Total, n = 459
Age [Years]	38 [31-44]
Clinical Stage	
I	322 (70%)
II	102 (22%)
III	35 (8%)
Clinical Stage ≧ IIC	37 (8%)
M-Stage (CSII/III)	
M0	436 (95%)
M1a	10 (2%)
M1b	13 (3%)
IGCCCG Risk Classification (CSII/III)	
Good	121 (88%)
Intermediate	16 (12%)
Initial treatment CS I (missing values: n=19)	
Active Surveillance	221 (73%)
Chemotherapy adjuvant (1x Carboplatin)	35 (11,5%)
Chemotherapy adjuvant (2x Carboplatin)	41 (13,5%)
Primary RPLND	1 (<0,5%)
Others	5 (2%)
Initial treatment CS II-III (missing values: n=2)	
Active Surveillance	3 (2%)
Chemotherapy	70 (52%)
Chemotherapy + PC-RPLND	15 (11%)
Radiotherapy	16 (12%)
Primary RPLND ± Chemotherapy adjuvant	23 (18%)
Others	7 (5%)

[1]Note: Continuous variables are presented as median [IQR], categorical variables are given as n (%). IGCCCG = International Germ Cell Cancer Collaborative Group.

Table 2a Baseline characteristics and initial treatment of relapsing clinical stage I patients (*n = 322*).

Patient characteristic	All relapses n = 65/322 (20%)	Relapse <12 months n =22/65 (34%)	Relapse >12 months n = 43/65 (66%)	p-value
Risk factors CS I (n=65)				
Rete testis infiltration (missing values: n=22)	14 (33%)	4 (31%)	10 (33%)	0.869
Tumor size >4cm (missing values: n=35)	9 (30%)	5 (46%)	3 (18%)	0.091
LVI+ (missing values: n=13)	9 (17%)	4 (22%)	5 (15%)	0.495
≥pT2 (missing values: n=6)	17 (29%)	8 (40%)	9 (23%)	0.174
Age (<30 years) (missing values: n=0)	8 (12%)	1 (5%)	7 (16%)	0.173
HCG (at orchiectomy) (missing values: n=26)	0,5 [0,1-3,4]	0,2 [0,1-21]	0,5 [0,1-3,4]	0.518
LDH (at orchiectomy) (missing values: n=26)	217 [183-244]	202 [180-244]	220 [197-245]	0.518
HCG (nadir after orchiectomy) (missing values: n=31)	0,2 [0,1-1,03]	0,1 [0,1-0,8]	0,5 [0,1-1,3]	0.209
LDH (nadir after orchiectomy) (missing values: n=34)	216 [181-234]	207 [181-241]	216 [185-232]	0.917
Initial treatment CS I (n=64, 1 patient treated with radiotherapy of the retroperitoneum)				0.860
CS I, Active Surveillance	51 (80%)	17 (81%)	34 (79%)	
CS I, Carboplatin	13 (20%)	4 (19%)	9 (21%)	0.764
1x Carboplatin	9 (69%)	3 (75%)	6 (67%)	
2x Carboplatin	4 (31%)	1 (25%)	3 (33%)	

[1]Note: Continuous variables are presented as median [IQR], categorical variables are given as n (%)

Table 2b Baseline characteristics and initial treatment of relapsing clinical stage II-III patients (*n = 137*).

Patient characteristic	All relapses n = 29/137 (21%)	Relapse <12 months n =16/29 (55%)	Relapse >12 months n = 13/29 (45%)	p-value
Clinical Stage ≧ IIC	10 (11%)	8 (21%)	2 (4%)	0.007
M-Stage				0.009
M0	88 (93%)	32 (84%)	56 (100%)	
M1a	2 (2%)	2 (5%)	0	
M1b	4 (5%)	4 (11%)	0	
IGCCCG Risk Classification				0.390
Good	25 (86%)	14 (81%)	12 (92%)	
Intermediate	4 (14%)	3 (19%)	1 (8%)	
Risk factors CS II-III (n=29)				
AFP (at chemo) (missing values: n=18)	2,7 [1,0-5,0]	1,0 [1,0-12,0]	2,2 [1,7-3,8]	0.613
HCG (at chemo) (missing values: n=18)	3,8 [0,2-30,3]	30,3 [3,5-62777]	1,4 [0,1-25,2]	0.030
LDH (at chemo) (missing values: n=18)	379 [188-881]	881 [340-2950]	249 [185-482]	<0.001
LDH 2xULN (at chemo) (miss. values: n=18)	8 (50%)	7 (70%)	1 (16%)	0.039
Initial treatment CS II-III (n=29)				0.199
Chemotherapy	24 (83%)	15 (94%)	9 (70%)	
Radiotherapy	1 (3%)	0	1 (7%)	
Primary RPLND ± Chemotherapy adj.	4 (14%)	1 (6%)	3 (23%)	

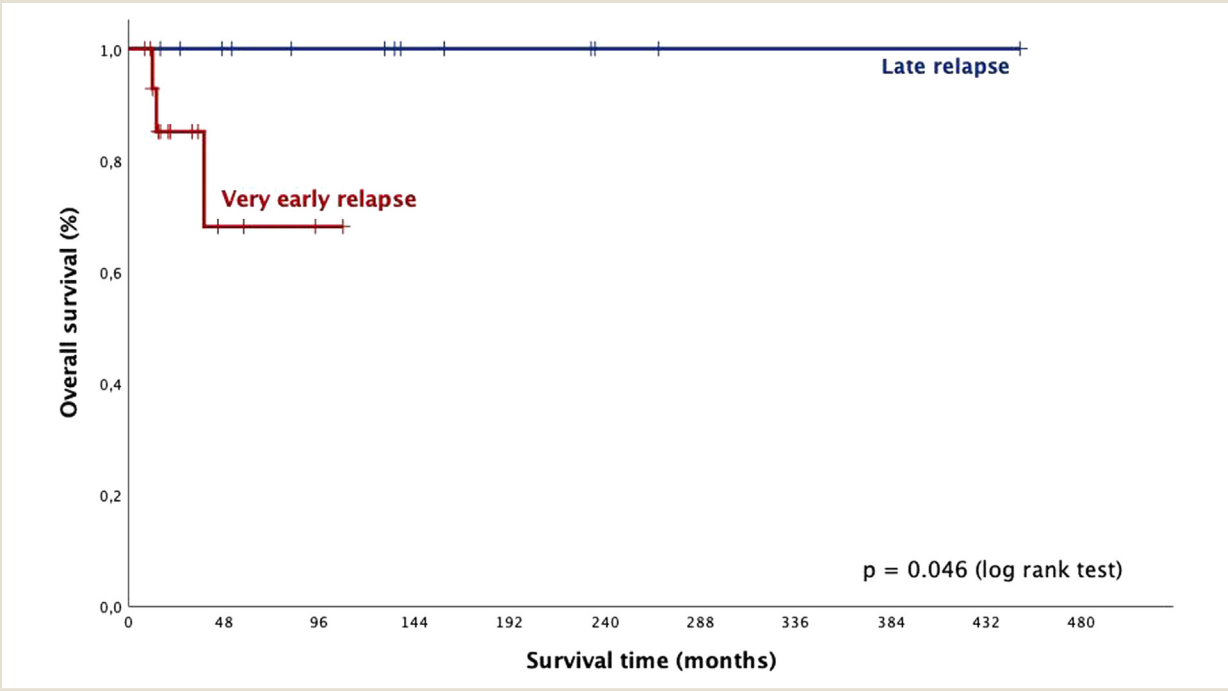
[1]Note: Continuous variables are presented as median [IQR], categorical variables are given as n (%). IGCCCG = International Germ Cell Cancer Collaborative Group.

Table 3a Description of relapse after initial clinical stage I (*n = 65*).

Patient characteristic	All relapses n = 65/322 (20%)	Relapse <12 months n =22/65 (34%)	Relapse >12 months n = 43/65 (66%)	p-value
Clinical Stage ≧ IIC of relapse (missing values: n=2)	29 (46%)	6 (21%)	23 (79%)	0.029
IGCCCG Risk Classification of relapse (missing values: n=2)				1.000
Good	57 (90%)	19 (90%)	38 (88%)	
Intermediate	6 (10%)	2 (10%)	4 (12%)	
Amount of Relapses (missing values: n=2)				0.256
1	53 (84%)	20 (91%)	33 (81%)	
2	7 (11%)	2 (9%)	5 (12%)	
≧3	3 (5%)	0 (0%)	3 (7%)	
Localisation of relapse (multiple answers possible)				0.849
Lymph nodes retroperitoneum	51 (76%)	18 (78%)	33 (75%)	
Lymph nodes outside retroperitoneum	13 (19%)	4 (18%)	9 (20%)	
Lung	2 (3%)	1 (4%)	1 (2,5%)	
Bone	1 (2%)	0	1 (2,5%)	
Relapse treatment (missing values: n=2)				0.852
Chemotherapy	39 (62%)	12 (57%)	27 (64%)	
Primary RPLND	19 (30%)	7 (33%)	12 (29%)	
Chemotherapy + PC-RPLND	5 (8%)	2 (10%)	3 (7%)	

[1]Note: Categorical variables are given as n (%). IGCCCG = International Germ Cell Cancer Collaborative Group.

Figure 1 Kaplan-Meier estimates for overall survival of patients with initial clinical stage II-III comparing patients with early and later relapse ($n = 29$).



ing patients with de novo clinical stage I did not show any difference regarding OS ($P = .466$, data not shown).

Discussion

In this study, we found a risk of relapse of 20% for seminoma patients. Comparing very early (< 12 months after successful treatment) and later relapse, overall survival was significantly reduced in very early relapsing seminoma patients with de novo clinical stage II to III. Furthermore, these patients showed higher metastatic burden and tumor marker levels at the time of orchiectomy in very early relapsing patients compared to later relapses. Patients with de novo stage I did not show any survival differences.

Our described relapse rate is in line with the current literature. Approximately 15% of clinical stage I seminoma patients harbor subclinical metastatic disease and will thus relapse after orchiectomy alone. In our cohort of clinical stage I patients, 20% relapsed, but we could not identify any of the new risk factors from the DATECA (rete testis invasion, LVI+, LDH-elavation, HCG-elevation) or EAU risk classification (tumor size, rete testis invasion, LVI+) models to be a risk factor in the prediction of relapse (Table 2), however these results might be influenced by the small sample size.[6,7] Furthermore, the new risk classification models evaluated relapse at a later time point.[6,7]

In the de novo metastatic stage, relapse rates after radiotherapy for stage IIA/B seminoma has been reported with 9% to 24%, while 10% to 50% of all TGCT relapse after chemotherapy.[1] Trials evaluating newer treatment options as a primary RPLND or a combination of radiotherapy and carboplatin-based chemotherapy revealed lower rates of relapse in clinical stage IIA-B seminoma patients. On the 1 hand, several phase II trials analyzing a primary RPLND in seminoma patients, eg, the SEMS trial, the PRIMETEST trial as well as the COTRIMS trial, showed relapse rates ranging from 10% to 30%.[8-10] On the other hand, the single-arm, phase 2 SAKK 01/10 trial evaluated 1 cycle of carboplatin (area under the curve 7) followed by involved-node radiotherapy (30 Gy in 15 fractions for stage IIA disease and 36 Gy in 18 fractions for stage IIB disease) and showed a 3-year progression-free survival of 95.2% (CS IIA) and 92.6% (CS IIB).[11] However, in our cohort of patients none was treated using radiotherapy plus carboplatin.

However, the definition of early relapse is controversial. Most studies analyzing relapses in TGCT focus on a comparison of early relapse, which is mostly defined as relapse < 2 years after completion of primary treatment, and late relapse, being regularly described as relapse > 2 years after initial treatment. In our study, we focused on relapse occurring < 12 months after primary treatment, as patients developing recurrence that quickly, seem to be a particularly sensitive cohort of patients at risk. Furthermore, most analyses of relapse include a mixed population of seminomatous and nonseminomatous TGCT (NSGCT), mainly focusing on late relapse in NSGCT.[12,13] Currently only very few clinical studies are available analyzing relapses in seminoma patients. To the best of our knowledge, our study is the first dedicated to very early relapses in seminoma patients, which are defined as recurrence < 1 year after the completion of initial treatment.

As very early relapsing patients after de novo clinical stage II-III suffered from a reduced overall survival in our cohort of patients, it

Table 3a Description of relapse after initial clinical stage II-III ($n = 29$).

Patient characteristic	All relapses n = 29/137 (21%)	Relapse <12 months n =16/29 (55%)	Relapse >12 months n = 13/29 (45%)	p-value
Clinical Stage ≧ IIC of relapse (missing values: n=5)	18 (75%)	10 (56%)	8 (44%)	0.813
Amount of Relapses				0.045
1	22 (76%)	9 (56%)	13 (100%)	
2	3 (10%)	3 (19%)	0 (0%)	
≧3	4 (14%)	4 (25%)	0 (0%)	
Localisation of relapse (multiple answers possible)				0.563
Lymph nodes retroperitoneum	16 (52%)	9 (60%)	7 (44%)	
Lymph nodes outside retroperitoneum	8 (26%)	3 (20%)	5 (31%)	
Lung	4 (13%)	3 (20%)	1 (6%)	
Bone	1 (3%)	0	1 (6%)	
Peritoneum	2 (6%)	0	2 (13%)	
Relapse treatment (missing values: n=2)				0.973
Chemotherapy	13 (48%)	8 (50%)	5 (46%)	
Primary RPLND ± Chemotherapy adj.	7 (26%)	4 (25%)	3 (27%)	
Chemotherapy + PC-RPLND	7 (26%)	4 (25%)	3 (27%)	

[1]Note: Categorical variables are given as n (%). IGCCCG = International Germ Cell Cancer Collaborative Group.

is important to mention that this group of patients showed a significantly higher number of clinical stage and M-stage as well as higher HCG levels and LDH levels compared to patients with later relapse. These findings are in line with prior analyses, showing LDH and HCG at start of chemotherapy to be an important risk factor for poor outcome.[5,14] In line with a new proposal for the IGCCCG classification, LDH at a cut-off of 2.5 × upper limit of normal at start of chemotherapy was confirmed as an additional adverse prognostic factor in our cohort of metastatic seminoma patients.[5,14] As a result, patients at risk should be very closely monitored and relapse should ideally be treated at a referral centre. Basis of this recommendation is a higher risk of nonguideline concordant treatment at low volume centres.[15]

The predominant site of relapse was the retroperitoneal space. Interestingly, the site of relapse was not different regarding clinical stage or pretreatment, eg, adjuvant Carboplatin (20%; $n = 13$) or platinum-based chemotherapy (83%, $n = 24$). However, these results might be influenced by the small sample size. In our study, most relapses were subsequently treated by salvage chemotherapy, potentially followed by PC-RPLND, also primary RPLND was used as a treatment option in relapsing seminoma patients.[8,16] In line, our working group lately showed that RPLND in as primary treatment for low volume metastatic seminoma might result in high cure rates at midterm follow-up and is associated with a low frequency of treatment-associated morbidities, making this approach a feasible alternative to radiation therapy or systemic chemotherapy.[9]

Considering the drawbacks for conventional diagnostics included standard tumor marker (AFP, ß-HCG, LDH) in follow-up analyses, ongoing trials are evaluating novel tumor marker such as miRNA371-a-3p which showed promising results with higher sensitivity and specificity for patients experiencing relapse compared to the standard tumor marker.[17,18] However, postorchiectomy miRNA371 levels were not predictive of relapse in a recent publication, and there was no significant earlier relapse detection with the test.[19] Furthermore, radiomics–based machine learning classifier showed promising results regarding the prediction of histopathology of resected lymph nodes and might consequently be added to the diagnostic armamentarium of follow-up analyses in the near future.[20] Furthermore, a more detailed pathohistological evaluation of the orchiectomy as well as the RPLND specimens might be able to predict very early relapse, as seminoma might harbour yolk sac tumor elements, which are known to be associated with a worse prognosis. Therefore, our working group currently performs molecular and immunohistochemical analyses of orchiectomy specimens of our seminoma patients to further elucidate this issue. Nevertheless, lifelong alertness of the patient and treating physicians regarding potential relapses is clearly beneficial. After 5 years, regular health examinations should be set depending on each patient's risk profile.[1]

The limitations of our study include its retrospective design as well as the relatively short follow-up, missing to reach a median overall survival. Furthermore, multivariate analysis could not be performed due to the small numbers of deaths. As it is a single-center series, our findings need validation in an independent cohort. In order to further corroborate with the beforementioned findings, we intend to initiate a national register study to be realized within the German Testicular Cancer Study Group.

Conclusions

Taken together, our study, revealed that relapse occurred in 20% of all seminoma patients. In the de novo metastatic stage, very early relapse was associated with a higher metastatic burden and worse prognosis at the time of orchiectomy compared to later relapses, leading to a reduced overall survival in very early relapsing seminoma

patients compared to later relapsing patients. As a result, very early relapsing patients with de novo clinical stage II-III are of special interest to treating physicians, as they portray a worse prognosis.

Clinical practice points

Characteristics and outcome associated with relapse in seminomatous testicular germ cell tumors (STGCT) are still unclear. In a retrospective analysis including 459 patients, differences between very early relapse (VER) and later relapse (LR) were evaluated. VER was defined as tumour recurrence < 12 months after successful treatment.

Our findings suggest that relapse in seminoma occurred in 20% of all patients. Furthermore, very early relapse in de novo metastatic seminoma is associated with a higher metastatic burden at diagnosis as well as a reduced overall survival.

Consequently, treating physicians should be aware of these patients portending a dismal prognosis, so that an early intensification of systemic treatment needs to be discussed.

Ethical Statement

The authors have no ethical conflicts to disclose.

Disclosure

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

Pia Paffenholz: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **F. Seelemeyer:** Writing – review & editing. **Ruben Gößmann:** Writing – review & editing. **Melanie von Brandenstein:** Writing – review & editing. **David Pfister:** Writing – review & editing, Supervision. **Axel Heidenreich:** Writing – review & editing, Supervision, Conceptualization.

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