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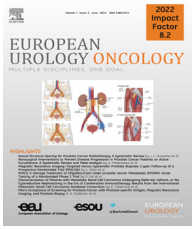

European Association of Urology

Prognostic Factor Risk Groups for Clinical Stage I Seminoma: An Individual Patient Data Analysis by the European Association of Urology Testicular Cancer Guidelines Panel and Guidelines Office

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Abstract

Background: The relapse rate in patients with clinical stage I (CSI) seminomatous germ cell tumor of the testis (SGCTT) who were undergoing surveillance after radical orchidectomy is 4–30%, depending on tumor size and rete testis invasion (RTI). However, the level of evidence supporting the use of both risk factors in clinical decision-making is low.

Objective: We aimed to identify the most important prognostic factors for relapse in CSI SGCTT patients.

Design, setting, and participants: Individual patient data for 1016 CSI SGCTT patients diagnosed between 1994 and 2019 with normal postorchidectomy serum tumor marker levels and undergoing surveillance were collected from nine institutions.

Outcome measurements and statistical analysis: Multivariable Cox proportional hazard regression models were fit to identify the most important prognostic factors. The primary endpoint was the time to first relapse by imaging and/or markers. Relapse probabilities were estimated by the Kaplan-Meier method.

Results and limitations: After a median follow-up of 7.7 yr, 149 (14.7%) patients had relapsed. Categorical tumor size ($\leq$2, >2–5, and >5 cm), presence of RTI, and lymphovascular invasion were used to form three risk groups: low (56.4%), intermediate (41.3%), and high (2.3%) risks with 5-yr cumulative relapse probabilities of 8%, 20%, and 44%, respectively. The model outperformed the currently used model with tumor size $\leq$4 versus >4 cm and presence of RTI (Harrell's C index 0.65 vs 0.61). The low- and intermediate-risk groups were validated successfully in an independent cohort of 285 patients.

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Conclusions: The risk of relapse after radical orchidectomy in CSI SGCTT patients under surveillance is low. We propose a new risk stratification model that outperformed the current model and identified a small subgroup with a high risk of relapse.
Patient summary: The risk of relapse after radical orchidectomy in patients with clinical stage I seminomatous germ cell tumor of the testis is low. We propose a new risk stratification model that outperformed the current model and identified a small subgroup with a high risk of relapse.

1. Introduction

Testicular cancer (TC) is the most common solid cancer in men aged between 14 and 34 yr, and 95% are germ cell tumors, that is, nonseminomatous germ cell tumor of the testis (NSGCTT) or seminomatous germ cell tumor of the testis (SGCTT). Approximately 70% of SGCTT patients present with clinical stage I (CSI) disease and have excellent survival outcomes [1]. The relapse rate after radical orchidectomy without adjuvant treatment varies between 4% and 30%, depending on pathological risk factors in the orchidectomy specimen [2]. The risk factors used in clinical practice to guide adjuvant treatment strategies are tumor size >4 cm and rete testis invasion (RTI) [1], whereas lymphovascular invasion (LVI) is a well-established risk factor in NSGCTT [3]. The 5-yr relapse-free survival ranged from 86.6% to 95.5% versus from 73% to 82.6% for patients with tumors $\leq$4 versus >4 cm, and from 86.0% to 92.0% versus from 74.9% to 79.5% for patients without versus with RTI present [4,5]. For CSI SGCTT, guidelines recommend active surveillance as the preferred strategy with the aims to reduce overtreatment as >70% of patients are cured by orchidectomy alone, and to reduce the risk of long-term toxicity induced by adjuvant external beam radiotherapy (EBRT) or chemotherapy. Long-term TC survivors experience increased mortality rates due to previous chemotherapy or radiation exposure [6]. EBRT to the retroperitoneum is associated with an increased risk of second malignancies [7].

Although the risk of relapse after orchidectomy is correlated with the tumor size, no optimal cutoff size has been determined [4,5,8]. The 4-cm cutoff size was derived from a cohort of 148 CSI SGCTT patients diagnosed between 1984 and 1991 with that median tumor size [9,10]. In contemporary series, the median tumor size was <4 cm; nowadays, patients present with smaller lesions at an earlier time point [11–14]. In addition, RTI was not well defined in studies in terms of its prognostic value, and studies were hampered by heterogeneity in design and had a high risk of bias [4,5,15]. Furthermore, "pagetoid" versus stromal RTI was not reported consistently, whereas the presence of either of these two entities might be of prognostic importance. As a result, the European Association of Urology Testicular Cancer Guidelines Panel concluded that the level of evidence was too low to support the routine use of tumor size and RTI as prognostic factors in clinical decision-making in CSI SGCTT patients [16].

To overcome the above limitations on the association between prognostic factors and the risk of relapse in CSI SGCTT patients undergoing surveillance after orchidectomy, we conducted an individual patient data (IPD) analysis to accurately identify risk factors and develop risk categories for relapse.

2. Patients and methods

2.1. Study cohort

IPD were retrospectively collected for patients from nine institutions. Eligible patients had to have primary unilateral CSI SGCTT with normal serum tumor marker (STM) levels of β-human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH) 4 wk after orchidectomy, be undergoing active surveillance, and have a minimum follow-up of 12 mo after orchidectomy. Imaging and STM assessment had to be performed at regular intervals during follow-up, in line with clinical guidelines. Patients with a spermatocytic tumor, with increased or elevated levels of serum β-hCG 3 wk after orchidectomy, or with elevated preorchidectomy serum levels of α-fetoprotein were not eligible. Centers provided their lower and upper limits of normal values of STMs. All patients had imaging of the thorax and abdomen within 4 wk of orchidectomy. In the presence of borderline enlarged retroperitoneal lymph nodes, patients were excluded if restaging after 6 wk showed retroperitoneal metastases. Patients with unknown preorchidectomy STM levels, tumor size, or RTI were excluded. A central pathology review was not performed; however, 53% of the cases were reviewed in the participating centers by a reference genitourinary pathologist. RTI was scored positive when stromal and/or pagetoid invasion was present in the orchidectomy specimen. Multifocality was defined if more than one testicular tumor was identified. Tumor size was defined as the largest diameter of the (largest) malignant lesion.

The study protocol with the predefined list of variables was approved by the European Association of Urology Guidelines Office. Patients were pseudonymized at the corresponding centers. The standardized database template was stored locally and filled on site. A secure environment compliant with the EU General Data Protection Regulations was guaranteed by each center. Data were checked by two reviewers (J.B. and R.S.) for ineligibility and missing data on key variables.

2.2. Statistical methods

The primary objective was to determine the prognostic importance of tumor size and RTI, alone and in combination with age, preorchidectomy β-hCG levels, LVI, and tumor

focality on the primary endpoint. A secondary objective was to construct prognostic risk groups that could serve to guide adjuvant treatment decision-making and follow-up.

The primary endpoint was the time to first relapse, measured from the date of orchidectomy to the date of first relapse assessed by imaging or STM elevation. Patients without a relapse were censored at the date of last imaging or STM level assessment. Relapse was defined as lymph node or distant metastasis on conventional, computed tomography, or magnetic resonance imaging, either with or without elevated levels of β-hCG or LDH, but histological confirmation was not mandatory. Levels of β-hCG above the normal upper limits were considered a relapse. An isolated elevation of LDH without metastases at imaging or a subsequent contralateral testis tumor was not considered a relapse. The secondary endpoints included the time to first radiological relapse and the time to first STM relapse.

Multivariable Cox proportional hazard regression models stratified by the institution were fit to the time to first relapse, using a step-down technique. Internal validation was performed by generating 500 bootstrap random samples with replacement. Model discrimination was assessed using Harrell's C index ($0 \leq C \leq 1$), which is the probability that for two patients chosen at random, the patient who relapses first has a higher probability of relapse according to the model [17].

Based on their coefficients in the multivariable Cox models, a weight for each level of each variable was obtained. The weights that corresponded to a given patient's characteristics were summed. Patients were divided into three risk groups according to their total score: low, intermediate, and high risk. Cut points were chosen with the goal of identifying low- and high-risk patients based on their observed 5-yr cumulative probabilities of relapse <10% and >25%, respectively. Kaplan-Meier time to relapse curves and observed 1- and 5-yr cumulative probabilities of relapse were obtained. Statistical analyses were carried out using Stata v16.1.

Assuming that a maximum of six variables would be included in the model and with the goal to observe 15 relapses per variable, 90 relapses would be required. We aimed to include a minimum of 600 patients for a relapse rate of 15% and a maximum of 1200 patients for a relapse rate of 7.5%.

A separate independent cohort of 285 CSI SGCTT patients undergoing active surveillance with a minimum follow-up of 12 mo from the Swiss Austrian German Testicular Cancer Cohort Study was used to externally validate the results.

3. Results

3.1. Patient population

IPD were received for 1036 patients. After quality control, 20 patients were excluded for ineligibility or missing data, leaving 1016 CSI SGCTT patients diagnosed between February 1994 and January 2019 for the analysis (Supplementary Table 1).

Patient and tumor characteristics are provided in Table 1. The median age and tumor size were 36 yr (interquartile range [IQR] 30–42) and 3.2 cm (IQR 2.0–4.5), respectively. The primary tumor size was ≤4 cm in 699 patients (69%), and 375 (37%), 125 (12%), and 844 (83%) had RTI, LVI, and normal baseline β-hCG, respectively. When known, 649 patients (87%) had normal baseline LDH, 104 (13%) had multifocal tumors, and 619 (84%) had concomitant germ cell neoplasia in situ (GCNIS).

Table 1 – Patient demographics of two independent cohorts of clinical stage I seminoma patients undergoing active surveillance after radical orchidectomy

Variable	Discovery cohort (1016 patients)	Validation cohort (285 patients)
Age (yr), median (IQR)	36 (30–42)	38.1 (32–48)
Baseline AFP, *n* (%)		
Normal	1016 (100)	285 (100)
Baseline β-hCG, *n* (%)		
Normal	844 (83)	234 (82)
Elevated	172 (17)	51 (18)
Baseline LDH, *n* (%)		
Normal	649 (64)	221 (78)
Elevated	101 (10)	55 (19)
Unknown	266 (26)	9 (3)
Primary tumor size (mm), median (IQR)	32 (20–45)	31 (20–42)
Primary tumor size (cm), *n* (%)		
≤2	274 (27)	71 (25)
>2–3	230 (23)	71 (25)
>3–4	195 (19)	69 (24)
>4–5	136 (13)	33 (12)
>5–6	95 (9)	24 (8)
>6	86 (8)	17 (6)
Rete testis invasion, *n* (%)		
Absent	641 (63)	179 (63)
Present	375 (37)	106 (37)
Lymphovascular invasion, *n* (%)		
Absent	873 (86)	239 (84)
Present	125 (12)	42 (15)
Unknown	18 (2)	4 (1)
Multifocality, *n* (%)		
No	704 (69)	
Yes, 2 foci	67 (7)	
Yes, >2 foci	37 (4)	
Unknown	208 (20)	285 (100)
GCNIS, *n* (%)		
No	118 (12)	
Yes	619 (61)	
Unknown	279 (27)	285 (100)

AFP = α-fetoprotein; β-hCG = β-human chorionic gonadotropin; GCNIS = germ cell neoplasia in situ; IQR = interquartile range; LDH = lactate dehydrogenase.

3.2. Prognostic factors for time to first relapse

After a median follow-up of 7.7 yr, 149 (14.7%) patients relapsed: 104 identified by imaging alone, 44 by imaging together with an elevated STM, and one by an elevated STM alone. The majority of image-detected recurrences was in the retroperitoneal lymph nodes (n = 144, 97%); two patients (1%) had pulmonary metastases, whereas other sites of recurrences were mediastinum (n = 6), iliac fossa (n = 1), groin (n = 1), and epidural space (n = 1). Treatments for primary recurrent disease consisted of chemotherapy (n = 68, 46%), radiotherapy (n = 80, 54%), or surgery (n = 3, of whom two combined with chemotherapy). Chemotherapy regimens included bleomycin, etoposide, and cisplatin in 31 patients, and etoposide and cisplatin in

Table 2 – Multivariable models for relapse-free survival after radical orchidectomy in clinical stage I seminoma patients undergoing active surveillance (discovery cohort)

Variable	HR (95% CI) *p* value	HR (95% CI) *p* value	HR (95% CI) *p* value	HR (95% CI) *p* value
Tumor size	Two groups	Continuous	Two groups	Three groups
Continuous		1.02 (1.01–1.02)		
		$p < 0.001$		
≤4 cm	1		1	
>4 cm	1.52 (1.08–2.15)		1.43 (1.03–1.99)	
	$p = 0.017$		$p = 0.032$	
≤2 cm				1
>>2–5 cm				2.06 (1.25–3.40)
				$p = 0.005$
>5 cm				3.14 (1.79–5.50)
				$p < 0.001$
Rete testis invasion				
Absent	1	1	1	1
Present	2.0 (1.39–2.87)	1.97 (1.39–2.77)	1.94 (1.38–2.72)	1.93 (1.36–2.72)
	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Lymphovascular invasion				
Absent		1	1	1
Present		1.49 (0.99–2.25)	1.63 (1.07–2.46)	1.48 (0.97–2.25)
		$p = 0.055$	$p = 0.022$	$p = 0.066$
Harrell's C Index	0.61	0.64	0.61	0.65

CI = confidence interval; HR = hazard ratio.

Table 3 – Cumulative probability of relapse at 1 and 5 yr following radical orchidectomy for clinical stage I seminoma patients undergoing active surveillance (*n* = 998, discovery cohort), stratified according to the new risk stratification based on primary testicular tumor size, rete testis invasion, and lymphovascular invasion

Risk groups: 998 patients	Cumulative probability of relapse and 95% confidence interval	
	At 1 yr	At 5 yr
Low risk: 563 patients (56.4%)	0.04 (0.02–0.05)	0.08 (0.06–0.11)
TS ≤5 cm, no RTI, no LVI		
TS ≤2 cm, either RTI or LVI, but not both		
Intermediate risk: 412 patients (41.3%)	0.10 (0.08–0.14)	0.20 (0.16–0.24)
TS ≤2 cm, both RTI and LVI		
TS >2–5 cm, RTI and/or LVI		
TS >5 cm, not both RTI and LVI		
High risk: 23 patients (2.3%)	0.30 (0.16–0.53)	0.44 (0.27–0.66)
TS >5 cm, both RTI and LVI		

LVI = lymphovascular invasion; RTI = rete testis invasion; TS = tumor size.

34 patients. Surgery was a retroperitoneal lymph node dissection (*n* = 1), combined with lung surgery (*n* = 1) and a metastasectomy of a nonspecified site (*n* = 1). Eleven patients died, none from SGCTT, although one patient died from treatment-related toxicity.

Excluding 18 patients with unknown LVI, univariate 5-yr cumulative relapse probabilities according to tumor size, RTI, and LVI are provided in Supplementary Table 2. Univariate analyses did not suggest prognostic importance of baseline LDH, tumor multifocality, or the presence of GCNIS. As each of these three variables had at least 20% missing data and was not significant in the univariate analyses, these were excluded from the multivariable model. Patient age, continuous or categorical, and baseline β-hCG, normal versus elevated, were not significant in multivariable models containing tumor size, RTI, and LVI. Their inclusion did not increase the concordance index and thus were excluded from the final model.

Table 2 depicts multivariable analyses for three different categories of tumor size: continuous, ≤4 versus >4 cm, and ≤2 versus >2–5 versus >5 cm. Three groups achieved a higher C index than for two groups, 0.65 versus 0.61, similar to size as a continuous variable (0.64). To facilitate construction of risk groups, tumor size in three groups was retained. Although the hypothesis of proportional hazards was upheld both for the individual variables and globally, and the Cox model could be used to assess the prognostic importance of the variables, a nomogram based on the Cox multivariable model overestimated the longer-term risks of relapse. All but nine relapses (92.1%) occurred within the first 5 yr of follow-up. The observed rather than model-predicted probabilities of relapse have been used to construct the risk groups.

3.3. *Novel risk groups for relapse*

The clinical composition of the low-, intermediate-, and high-risk groups is depicted in Table 3. In total, 563 patients (56.4%) were classified as having a low risk, 412 (41.3%) as having an intermediate risk, and 23 (2.3%) as having a high risk, with corresponding 5-yr cumulative relapse probabilities of 0.08 (95% confidence interval [CI] 0.06–0.11), 0.20 (95% CI 0.16–0.24), and 0.44 (0.27–0.66), respectively (Fig. 1 and Table 3). Since all but one patient had a radiological relapse and only five patients had an imaging relapse after a marker relapse, similar results were obtained for the time to first radiological relapse. The results for STM relapse are provided in Supplementary Table 3 and Figure 1.

Baseline characteristics of the 285 patients included in the validation cohort were similar to those in the development cohort; however, follow-up was shorter with a median of 3.0 yr (IQR 1.55–4.55; Table 1). Thirty-five patients developed a relapse (12.2%). Applying the risk group definition to the validation cohort, the C index was 0.72. The

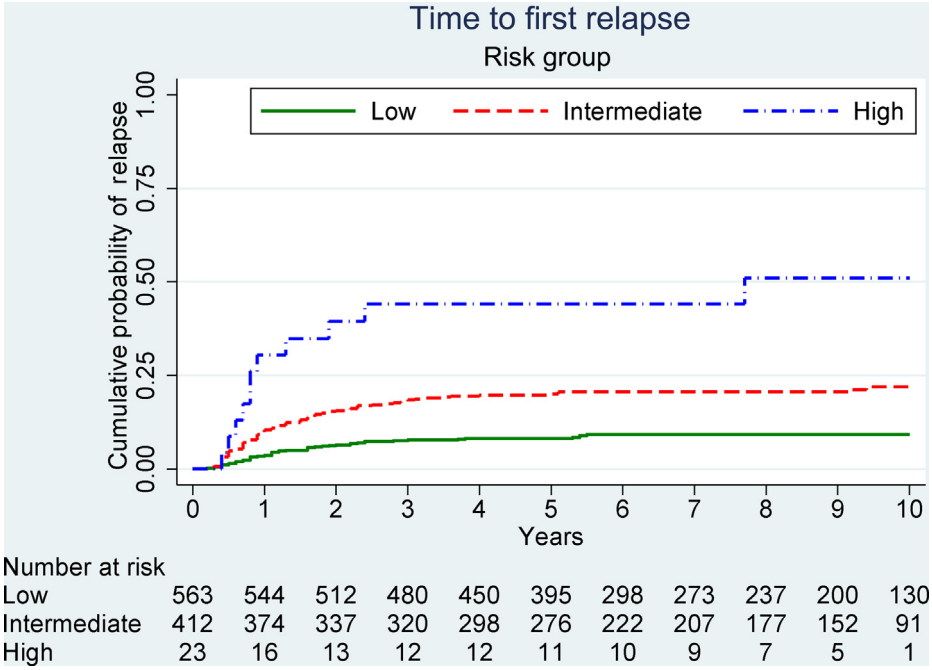

Fig. 1 – Cumulative probabilities of relapse of 998 patients with clinical stage I seminoma germ cell tumor of the testis undergoing active surveillance after radical orchidectomy (discovery cohort), stratified by prognostic factor risk groups based on primary testicular tumor size, rete testis invasion, and lymphovascular invasion.

Table 4 – Cumulative probability of relapse at 1 and 5 yr following radical orchidectomy for clinical stage I seminoma germ cell tumor of the testis patients in the validation cohort (*n* = 285), stratified according to the new risk stratification based on primary testicular tumor size, rete testis invasion, and lymphovascular invasion.

Risk groups: 285 patients	Cumulative probability of relapse and 95% confidence interval	
	At 1 yr	At 5 yr
Low risk: 162 patients (56.8%)	0.01 (0.00–0.05)	0.05 (0.02–0.11)
TS ≤5 cm, no RTI, no LVI		
TS ≤2 cm, either RTI or LVI, but not both		
Intermediate risk: 115 patients (40.4%)	0.14 (0.09–0.22)	0.25 (0.18–0.35)
TS ≤2 cm, both RTI and LVI		
TS >2–5 cm, RTI and/or LVI		
TS >5 cm, not both RTI and LVI		
High risk: 8 patients (2.8%)	NA	0.27 (0.08–0.72)
TS >5 cm, both RTI and LVI		

LVI = lymphovascular invasion; NA = not available; RTI = rete testis invasion; TS = tumor size.

cumulative probabilities of relapse at 1 and 5 yr were similar in the development and validation cohorts in the low- and very-low-risk groups, but the data were insufficient to validate the outcome in the high-risk group (see Tables 3 and 4, and Fig. 1 and 2).

4. Discussion

Our analysis identified three groups of CSI SGCTT patients with low, intermediate, and high risks of relapse. Based on tumor size (≤2, >2–5, and >5 cm), presence of RTI, and LVI, the 5-yr cumulative probabilities of relapse in the risk groups were 8%, 20%, and 44%, respectively. This new risk stratification was validated in an independent cohort of 285 CSI SGCTT patients.

The vast majority of CSI SGCTT patients are cured by orchidectomy. In unselected patients, however, 15–20% have subclinical metastases, predominantly in the retroperitoneum, and these patients relapse mainly in the first 3 yr after orchidectomy [18]. Adjuvant EBRT to the retroperitoneum or carboplatin chemotherapy reduces the risk of relapse [13,19–21], but active surveillance is recommended as the preferred strategy because survival remains very high, regardless of whether adjuvant treatment is given. Moreover, this young population has long life expectancy, and minimizing the risk of long-term toxicity and second malignancies stemming from adjuvant chemotherapy or EBRT is important. Historically, the risk of relapse appears to be driven by tumor size and RTI, but evidence to justify using these prognostic markers in adjuvant treatment decisions is elusive [15].

Tumor size and RTI are assessed on the orchidectomy specimen, but the interpretation of both risk factors is hampered by a lack of standardization. Formalin fixing and paraffin embedding, and tangential slicing of the tumor can impact size assessment. In multifocal tumors, the size of the largest tumor is assumed to be most relevant despite little evidence to justify this. The risk of relapse increases with tumor size: in tumors <3 cm, the risk of relapse was a maximum of 12% [22], whereas in large tumors (≥6 cm), the risk was 32% [13]. In clinical practice, size is dichotomized, with a cutoff of 4 cm being the most widely used. However, this cutoff dates back to 1993, being the median tumor size in a series by Warde et al. [10]. Since then, mul-

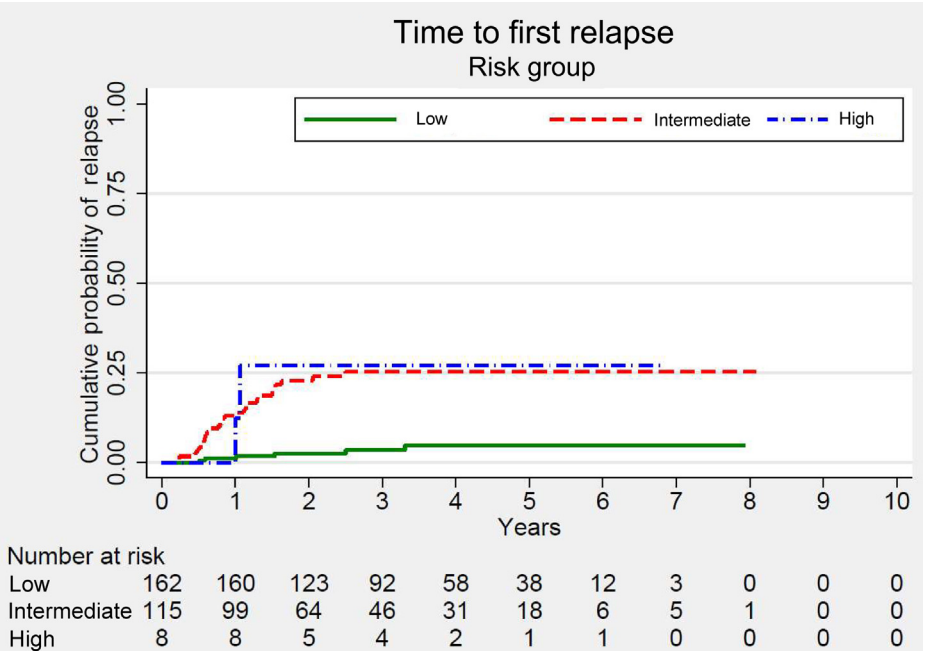

Fig. 2 – Cumulative probabilities of relapse of 285 patients with clinical stage I seminoma testis undergoing active surveillance after radical orchidectomy (validation cohort), stratified by prognostic factor risk groups based on primary testicular tumor size, rete testis invasion, and lymphovascular invasion.

tiple series have reported a median testicular tumor size of <4 cm (range: 2.0–3.8 cm), reflecting that the 4-cm cutoff is clinically less relevant. The current American Joint Committee on Cancer TNM classification includes a tumor size of 3 cm for T1a versus T1b SGCTT, with no impact on prognosis according to this size [23]. Lesko et al. [15] provided an overview of the different cutoffs used in the literature, but no optimal cutoff was identified. In the present study, 69% of the patients had a tumor size of ≤4 cm. We propose a new risk stratification model for primary tumor size based on cutoffs of ≤2, >2–5, and >5 cm, representing 27%, 55%, and 17% of our study population, respectively.

Evidence on the prognostic significance of RTI is hampered by a lack of clear definitions, that is, stromal versus pagetoid RTI; the proportion of missing RTI data in the literature is up to 50%, and the prevalence of RTI is 15–67%. In addition, the correlation between RTI and the risk of relapse is modest with a reported hazard ratio of 1.4–1.7 [4]. For the present study, missing RTI data were an exclusion criterion, and we identified 37% of the primary tumors having RTI present. A central pathology review, however, was not performed. Although 53% of the cases were reviewed by a reference genitourinary pathologist, whether RTI was stromal versus pagetoid or a combination of both was unknown in 330 of the 370 RTI-positive cases. LVI, which is known to be correlated with the risk of relapse in CSI NSGCTT, has not been identified previously as a risk factor in SGCTT. In the present population, 12% was LVI positive and was associated with the risk of relapse too. Taken together, 83% of patients in our study had tumors ≤5 cm, did not have both RTI and LVI present, and had 5-yr cumulative probabilities of relapse between 8% and 20%. Only a very small subgroup of CSI SGCTT patients, characterized by tumors ≥5 cm, with both RTI and LVI present, had a 5-yr cumulative probability of relapse of 44%, meaning that >50% is cured by orchidectomy alone. In discussions with the patient, incorporating potential risks and benefits and individual patient circumstances and preferences, active adjuvant treatment might be considered in this subgroup. Using the former risk stratification, the relapse rate with either tumor size >4 cm or RTI, or both was 15.5% in patients undergoing surveillance versus 9% in patients treated adjuvantly with carboplatin [19]. In addition, improved diagnostic strategies to detect occult metastatic disease in CSI SGCTT, such as sentinel node biopsy, might be of added value for clinical decision-making on adjuvant treatment [24]. Whether the new risk stratification could change clinical practice remains to be seen, as relapsing CSI SGCTT patients under surveillance are almost always cured by rescue treatment [18].

This study has limitations: due to its retrospective nature, data were missing for some variables. There was a lack of standardization of pathology reporting across centers, and no central pathology review was performed. Variability in tumor marker assays existed with different upper limit cutoffs. Despite a relatively small sample size of 285 cases and a shorter median duration of follow-up, the intermediate- and low-risk groups were validated in the validation cohort, but the high-risk group consisted of only eight cases with two relapses, precluding any conclusions. Further follow-up and more relapses are required to strengthen the validation.

5. Conclusions

The relapse rate in a surveillance cohort of CSI SGCTT patients (n = 1016) was 14.7%. Using IPD, we have built a new risk stratification model including tumor size (≤2,

>2–5, and >5 cm), presence of RTI, and LVI, which outperformed the current model with tumor size of >4 cm and RTI. The new model identified a very small subgroup of patients with a tumor size of >5 cm with both RTI and LVI present, who had a 5-yr cumulative relapse probability of 44%. Notwithstanding this small subgroup, almost all CSI SGCTT patients were categorized as having a low or intermediate risk of relapse according to our new model. This underpins that consideration of adjuvant treatment in CSI SGCTT patients seems justified only in a very limited proportion of patients, and active surveillance should remain the preferred adjuvant strategy.

Author contributions: Joost L. Boormans had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Boormans, Anson-Cartwright, Glicksman, Hamilton, Hahn, Daugaard, Lauritsen, Wagner, Avuzzi, Nicolai, del Muro, Aparicio, Stalder, Rothermundt, Fischer.
Analysis and interpretation of data: Sylvester, Boormans, Laguna.
Drafting of the manuscript: Boormans, Sylvester, Laguna.
Critical revision of the manuscript for important intellectual content: Nicolai, Hamilton, Daugaard, Aparicio, Wagner, Lauritsen, Fischer.
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Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.10.014.

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