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Late relapses in stage I testicular cancer patients on surveillance

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Abstract:

Background: Comprehensive data on late relapse (LR) and very late relapse (VLR) in patients with clinical stage I (CS-1) testicular cancer followed on surveillance are missing. These data are essential for the planning of optimal follow-up.

Objective: 1) assess incidence and outcome of LR (>2 years) and VLR (>5 years) in a large cohort of CS-1 surveillance patients and 2) examine differences in clinical characteristics of patients with early relapse (ER), LR and VLR.

Design, setting and participants: CS-1 surveillance patients diagnosed 1984-2007 were identified from the retrospective DaTeCa database.

Outcome measurements and statistical analysis: Survival and relapse probabilities estimated and compared with log-rank tests and Cox regression analyses. Differences in patient characteristics compared with chi-square, Fisher's exact, and Mann-Whitney tests.

Results and limitations: 3366 (2000 seminoma and 1366 nonseminoma) patients were included. Median follow-up: 15 years. Five-year conditional risk of LR: 5.0% and 2.1% for seminoma and nonseminoma patients, respectively. There were no significant differences in disease specific or overall survival when comparing the LR(+VLR) and ER patients by log-rank, but Cox regression adjusted for age showed a significant effect of time-to-relapse on survival for seminoma patients. Apart from significantly more ER nonseminoma patients with elevated hCG at relapse, there were no significant differences in patient characteristics at orchiectomy or relapse. Limitations include retrospective design and exclusion of patients offered adjuvant therapy.

Conclusion: The risk of VLR is minimal and the patients carry a good prognosis. Patient characteristics of CS-1 surveillance patients with LR(+VLR) do not differ significantly from patients with ER.

Patient summary: We compared stage I testicular cancer surveillance patients with early relapse with late relapsing (>2 years) patients. Late relapse patients as a group did no worse than early relapse patients, though increased time to relapse was negatively associated with survival for seminoma patients.

Introduction

Late relapse (LR) > 2 years after primary successful treatment for testicular cancer (TC) is a rare event. Data on clinical stage I patients (CS-1) followed on surveillance are sparse. The rate of LR for these patients is estimated to be 1-3%[1–4]. Most studies on late relapse for CS-1 patients are hampered by short follow-up, non-consecutive series of patients, and lack of descriptions of clinical outcome. Accordingly, the primary aim of the present study was to assess the incidence and clinical outcome for late relapsing chemotherapy-naïve patients in a large unselected cohort of CS-1 patients undergoing surveillance. The secondary aim was to examine differences in risk factors in patients with early (ER), late and very late relapses (VLR).

Patients and methods

From the DaTeCa database (supplemental file 1), we identified all CS-1 patients undergoing surveillance from 1984 through 2007 (*n* = 3774). Patients receiving adjuvant treatment (*n* = 373) and patients with synchronous bilateral testicular cancer (*n* = 35) were excluded, leaving 3366 patients for the present analysis.

All patients underwent primary inguinal orchiectomy followed by staging with measurements of tumour markers (TM): alpha fetoprotein (AFP), human chorionic gonadotropin (hCG), lactate dehydrogenase (LDH)), CT scan of the abdomen, and thoracic x-ray/CT scan.

Patients were offered five years of follow-up after orchiectomy and were included in the analyses irrespective of their adherence to the surveillance programme.

A core biopsy was performed at relapse except for some cases with clear progression on CT-scan and/or significant increase of TM. Patients with relapse were offered radiotherapy (seminoma stage IIA/B) or chemotherapy (bleomycin, etoposide, and cisplatin (BEP)). In case of residual tumour after chemotherapy, surgical removal of the tumour was performed.

Clinical data from time of orchiectomy and relapse were obtained from patient files and included in the DaTeCa database. Information on the DaTeCa database including data on prognostic factors for relapse and detection of relapses are thoroughly described in two previous papers[5,6]. Through linkage with several Danish Registries[7–10] we identified patients with relapse after termination of the follow-up programme and patients lost to follow-up. Data were updated November 30, 2012.

The following definitions of time to relapse were used: Early relapse (ER): relapse 0- 24 months after orchiectomy. Late relapse (LR): relapse 25-60 months after orchiectomy. Very late relapse (VLR): relapse after completing the 60-months follow-up program.

Statistics

Our primary aim was to access the incidence and clinical outcome of patients with late relapse. To estimate this, we calculated relapse- and survival probabilities by the Kaplan-Meier method. Patients were censored at time of emigration (*n* = 67), if lost from the Danish civil registers (*n* = 4), at time of a metachronous testicular cancer (*n* = 70), or at time of linkage to the national registries (November 30, 2012). Time to relapse was defined as time from date of orchiectomy until date of relapse diagnosis. Conditional survival estimates were used to assess the 5-year risk of LR by calculating the 5-years cumulative incidence of relapse, given the patients were relapse free for

the first two years of follow-up. Conditional 10-years risk of VLR was calculated as cumulative incidence given the patients were relapse-free during the five-year follow-up programme. Disease specific survival (DSS) and overall survival (OS) after relapse were calculated from date of first relapse until death from TC or treatment complications (DSS) or until death of any cause (OS). Median follow-up was calculated using the reverse Kaplan-Meier method with the status indicator (relapse) reversed[11]. To examine the specific relationship between time to relapse and DSS & OS, Cox proportional hazards regression models were constructed. The models included time from orchiectomy to relapse and age at relapse; with both variables added to the model using restricted cubic splines, with three to four knots, to account for nonlinearity. Due to the small number of VLRs, the groups LR and VLR were merged into one group comprising all patients relapsing after 24 months for subsequent analyses: LR(+VLR). Survival after relapse was compared between patients with ER and patients with LR(+VLR) using log-rank statistics.

To assess our second aim, differences in patient characteristics for ER and LR(+VLR), we used chi-square test or Fisher's exact test for categorical and Mann-Whitney U-test for continuous variables. The following characteristics were compared: age, tumour size, vascular invasion, invasion of rete testis, invasion of epididymis, AFP and hCG elevation at time of orchiectomy and at time of relapse as well as presence of embryonic carcinoma, endodermal sinus tumour, chorionic carcinoma and teratoma at time of diagnosis for nonseminoma patients.

All analyses were done separately for seminoma and nonseminoma patients. P-values were two-sided and considered significant when $p< 0.05$. Statistical analyses were performed using SPSS (Version 22.0. Armonk, NY: IBM Corp.) and R 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria, 2013).

Results

The final cohort consisted of 2000 patients with seminoma and 1366 patients with nonseminoma.

SEMINOMA PATIENTS

INCIDENCE AND OUTCOME

Median follow-up for patients was 15 years (inter quartile range (IQR): 9 - 21). A total of 388 patients relapsed with a median time to relapse of 13 months (IQR: 7 - 25); 288 had ER, 83 had LR and 17 relapsed after termination of the five years surveillance programme (VLR). The 2-year cumulative risk of ER was 14.5% (95% Confidence interval [CI]:13.0-16.9) (figure I).

The five-year conditional risk of LR was 5.0% (95% CI: 4.0-6.1) while the 10- year conditional risk of VLR was 1.0% (95% CI: 0.6-1.7).

Twelve seminoma patients died of TC or treatment complications: Four of the ER, one of the LR and two of the VLR died of disseminated disease, while three ER, one LR and one VLR patient died of treatment complications. One of the two VLR patients had nonseminoma histology in the relapse (table 3).

Comparing ER with LR(+VLR) patients by log-rank test, the two groups demonstrated no significant differences in DSS ($p = 0.13$) or OS ($p = 0.5$). For patients with LR(+VLR), ten years DSS and OS were 94.9% (95%CI: 88.1-97.8) and 89.3% (95% CI: 80.2-94.4), respectively.

Increasing time to relapse was significantly associated with worse DSS and OS after relapse, in an approximately linear fashion (p-values for linear effects 0.03 and 0.01, respectively, p-values for

non-linear effects 0.08 and 0.18). In the Cox regression model, 10-years DSS after relapse at two and five years were 98.5% (95%CI: 96.7-100) and 96.3% (95% CI: 92.8-99.9), respectively, for a patient 38 years old at time of relapse. The 10-years OS after relapse at two and five years were 98.2% (95% CI: 96.9-99.5) and 96.9% (95% CI: 94.6-99.3), respectively. The very small number of events following VLR did result in very uncertain estimates of the effect of late time to relapse on survival, however.

DIFFERENCES IN PATIENT CHARACTERISTICS

Table 1 shows patient characteristics at time of orchiectomy and table 2 summarizes the characteristics and treatment at time of relapse. Univariate analyses of patient characteristics at time of orchiectomy and at time of relapse did not show any significant differences between ER and LR(+VLR) (Supplemental table 2).

Eight of the LRs were detected at the final CT-scan at five years follow-up. All VLR were detected due to patient symptoms (stomach and back pain and enlarged cervical lymph nodes). Details of the 17 VLR are shown in table 3. The hCG level was increased in eight (47%) of these patients. Biopsies of their relapses revealed seminoma and none of the eight had elevated tumour markers at time of orchiectomy.

All relapsing patients were in the good prognostic group, apart from two patients with LR, who were in the intermediate prognostic group (one due to hCG level of 6975 IU/L and nonseminoma histology, the other due to bone metastases).

NONSEMINOMA PATIENTS

INCIDENCE AND OUTCOME

Median follow-up was 15 years (IQR: 10-22). In total, 424 patients relapsed; 400 had ER, 20 had LR, and four had VLR. Median time to relapse was 5 months (IQR: 3-10).

The 2-year cumulative risk of ER was 29.4% (95% CI: 27.1-31.9) (figure I) .The 5-year conditional cumulative risk of LR relapse was 2.1% (95% CI: 1.4-3.3) and the 10 year cumulative risk of VLR was 0.3% (95% CI: 0.1-1.1).

In total 15 of the nonseminoma patients died of TC or treatment complications: Nine ER patients died of progressive disease, while five ER patients and one LR patient died of treatment complications.

There was no significant effect of time to relapse on DSS or OS after relapse (all p-values >0.1); and visual inspection of the estimated relationships between time to relapse and DSS / OS showed no apparent effect, either. Similarly, log-rank comparison of ER versus LR(+VLR) was non-significant for both DSS (p = 0.8) and OS (p = 0.8). For LR(+VLR) ten years DSS and OS were 95.8% (95% CI: 73.9-99.4) and 89.8% (95% CI: 64.3-97.4), respectively.

DIFFERENCES IN PATIENT CHARACTERISTICS

Table 1 shows patient characteristics at time of orchiectomy and table 2 summarizes the characteristics at time of relapse. There were no significant differences in primary histology between the two groups. Likewise, we did not detect any significant differences in other patient characteristics between ER and LR(+VLR) at time of diagnosis. At time of relapse, more patients in the ER group than in the LR(+ VLR) group had increased levels of hCG (p=0.001) (Supplemental

table 2). Transformed teratoma was seen in two ER patients' residual tumours after BEP treatment.

Five of the LR were detected at the final five-year follow-up CT-scan. All VLR were detected due to patients' symptoms (stomach pain, back pain and shortness of breath). Details of the four patients with VLR are shown in table 3.

While the vast majority of relapses were in the good prognostic group, 3 (15%) of the LRs and 17 (4%) of the ERs were in the intermediate group. Poor prognosis was only seen in three ER patients. Details of treatment are found in table 2.

Discussion

In this large study of 3366 CS-1 patients followed on surveillance, we found a conditional 5-year cumulative risk of LR of 5.0% for seminoma patients and 2.1% for nonseminoma patients. Comparing the two groups by log-rank, there were no significant differences in DSS or OS for ER versus LR(+VLR) patients. However, for seminoma patients we found a significant association between time to relapse, considered as a continuous variable, and DSS and OS. We found no significant differences in patient characteristics at time of orchiectomy and at time of relapse in ER versus LR(+VLR), apart from more ER nonseminoma patients with elevated hCG at time of relapse.

With more than 15-years follow-up and 124 late relapses, the present study adds substantial information on both patient characteristics and survival for LR and VLR surveillance patients. We have not been able to identify any long-term studies with comparable data on the incidence of LR.

The largest study of LR in patients on surveillance included 28 patients and was not able to calculate the incidence of LR[12].

A study from Memorial Sloan-Kettering Cancer Center reported a five-year cancer specific survival of 93% in 18 chemotherapy-naïve patients with LR[13]. This is in line with our results. Fedyanin et al. analyzed data on 169 relapsing chemotherapy-naïve stage 1 patients, including 29 patients with LR[14]. They found significantly worse outcome for seminoma patients with LR: Three year OS was 91% and 65% for ER and LR, respectively. There were no significant differences in OS for the nonseminoma patients. In the present study, three of the VLR seminoma patients died of progressive disease or complications. All were in the good prognostic group and none of them had comorbidity that could explain the outcome for these patients, but one of them had nonseminoma histology in the relapse. Increasing time to relapse resulted in reduced DSS and OS for seminoma patients; however, with only five disease related deaths and 13 deaths overall among the LR(+VLR) seminoma patients, these results regarding effects of time to relapse should be interpreted with caution.

A large part of the VLR seminoma patients (47%) had elevated hCG at time of relapse. This finding is in line with a study of surgical management of LR in CS-1 patients on surveillance, which also identified hCG as the predominant tumour marker at relapse[12], however, only two of the patients in that study had seminoma. A study of LR in nonseminoma CS-I patients undergoing surveillance concluded that seminoma was the predominant histology at relapse in 56% of 9 relapses[4]. We could not confirm this finding in the present study. Nonseminoma histology was predominant in most relapse biopsies (67%) of LR(+VLR) in nonseminoma patients.

Various studies advocate for long, even lifelong, follow-up for the surveillance patients[13,15–18]. In the present study the 10-year cumulative risk of relapse for seminoma patients without relapse during the 5-years follow-up programme was 1%. Accordingly, in a surveillance setting with annual CT scans, approximately 100 patients would need an annual scan for five years to detect one relapse. This is not only costly; it also adds a significant burden to the patients and the hospitals. The potential risk of second cancers after repeating CT-scans in this group of patients is controversial[19–21]. Additionally, the risk of dying of other causes will by far exceed the risk of dying of TC for these individuals. Hence, we agree with the authors of the Kollmannsberger study[1] that extending surveillance imaging schedules for all - for the benefit of the few - may not add overall value.

The few relapses after five years follow-up were all diagnosed due to patient symptoms. Consequently, it is of utmost importance to educate patients and general practitioners on the risk of VLR to avoid treatment delay. Measurement of tumour markers beyond five years follow-up in patients with a history of CS-1 might be valuable but is not sufficient on its own as half of the VLR did not have elevated tumour markers at time of relapse in the present study.

The retrospective nature adds some limitations to our study. Early in the study period, 384 seminoma patients (most with tumour size > 6 cm) received adjuvant treatment (not included in the present study). Thus, the relapse rate for seminoma patients could possibly have been higher with these patients included. On the other hand, this is by far the largest study of LR in CS-1 surveillance patients. The very long follow-up and the population-based nature of the study add strength to the applicability to other surveillance populations.

Conclusion

Chemotherapy-naïve surveillance patients with LR(+VLR) have a good prognosis and their characteristics do not differ from patients with ER. We believe that patients with LR(+VLR) safely can be managed by following the general recommendations for relapsing CS-1 patients[22]. The conditional risk of VLR is minimal, nevertheless patients and physicians should be aware of this risk to minimize treatment delay. Future studies should focus on the optimal follow-up programme for CS-1 patients.

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298 **Figure legends:**

299 Figure 1: Cumulative incidence of relapse from time of orchiectomy.

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