Testis Cancer

A Nationwide Cohort Study of Stage I Seminoma Patients Followed on a Surveillance Program

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1. Introduction

Conventional treatment with adjuvant radiotherapy for stage I seminoma has resulted in excellent cure rates. However, focus on morbidity and late effects, in particular the risk of secondary cancers, has made the continued use of adjuvant radiotherapy less attractive. An increasing number of guidelines now recommend surveillance as the preferred management option [1–5], but recent studies document that current patterns of care for stage I seminoma are still highly variable [6,7].

In 1984, a surveillance program for Danish patients with stage I seminoma was established. The current study presents the largest group of stage I seminoma patients followed on a surveillance program.
ever reported with long-term follow-up and detailed information on relapses, prognostic factors, and treatment.

2. Patients and methods

From the Danish testicular cancer (DaTeCa) database (Supplement), we retrospectively identified 2378 patients with stage I seminoma diagnosed between January 1, 1984, and December 31, 2007. Patients eligible for the study had no history of testicular cancer. Exclusion criteria were human chorionic gonadotropin (hCG) levels >200 IU/L, adjuvant treatment, and synchronous testicular cancer (Fig. 1).

Primary surgery in all patients consisted of inguinal orchiectomy followed by staging with the tumor markers (TM) α-fetoprotein, hCG, and lactate dehydrogenase (LDH); a computed tomography (CT) scan of the abdomen; and a chest x-ray or CT scan. Patients with increased hCG and/or LDH levels at the time of orchiectomy had weekly measurements of TMs until normalization, confirming stage I disease.

All patients were offered 5 yr of follow-up (Fig. 2). During the study period, modest changes in the follow-up program were introduced. Patients who missed their follow-up appointments received two standard reminder letters as well as a personal letter before they were removed from the surveillance program. In addition, a note was sent to the patient’s general practitioner. All treated patients were included in the analyses irrespective of their adherence to the surveillance program.

Relapsing patients with retroperitoneal lymph node metastases ≤5 cm (stage IIa and IIb) were offered radiotherapy. However, in recent years, only stage IIa and IIb retroperitoneal lymph node metastases <3 cm have been eligible for radiotherapy. The remaining relapsing patients were treated with bleomycin, etoposide, and cisplatin (BEP). Initially, four cycles of BEP were administered, but after 2001, patients belonging to the good prognostic group [8] received only three cycles of BEP.

Clinical data on patients, relapses, and possible prognostic factors were collected through review of patient files and pathology reports. Pathology data included tumor size, invasion of rete testis, epididymis (EPI), small vessels (vascular and/or lymphatic) (VI+), and invasion of tunica albuginea, as well as histology at relapse.

Patients were followed for late relapse through the Cancer Registry [9], the Danish Pathology Register, and the Danish National Patient Register [10]. Information about survival and cause of death was obtained from the Danish Register of Causes of Death [11]. Data on death and vital status were updated on November 30, 2012, and crosschecked with patient files and pathology reports.

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Fig. 1 – Consolidated Standards of Reporting Trials diagram. The three patients receiving surgery only had local relapse in the scrotum (n = 2) and a retroperitoneal teratoma (n = 1). The latter patient received retroperitoneal lymph node dissection. *One patient died of sepsis during BEP treatment.

*One patient was treated with surgery for abdominal relapse with mature teratoma. His second relapse was treated with BEP. The patient died of bleomycin pneumonitis. One patient initially was treated with surgery for a local relapse in scrotum. His second relapse was treated with radiotherapy plus BEP. The patient died of pulmonary edema during BEP treatment. #One patient initially received radiotherapy for relapse and died of sepsis during transplantation (salvage treatment for his second relapse). One patient progressed with liver metastasis after receiving radiotherapy for his first relapse. He developed bleomycin pneumonitis after BEP treatment for his second relapse and died of circulatory collapse.

Adj = adjuvant; BEP = bleomycin, etoposide, and cisplatin; GCC = germ cell cancer; hCG = human chorionic gonadotropin; NED = no evidence of disease.
The present analysis includes 1954 patients with stage I seminoma. Patient characteristics are shown in Table 1. Median follow-up time was 15.1 yr (range: 0.6–28.7 yr). Relapse was observed in 18.9% (369 of 1954) of the patients after a median time of 13.7 mo (range: 2.3–173.6 mo). During the first 2 yr after orchectomy, 73.4% (271 of 369) of relapses were detected, 22.2% (82 of 369) relapsed between years 3 and 5, and 4.3% (16 of 369) relapsed >5 yr after orchectomy (Fig. 3).

Of 353 patients who experienced relapse during the 5-yr follow-up period, 74.8% (264 of 353) of the relapses were detected by radiology (CT scan, ultrasound, or x-ray) and 19.5% by radiology plus TMs (69 of 353 patients) (Fig. 3). Physical examination detected 5.1% (18 of 353) of relapses and three relapses were revealed by elevation of TM levels only.

Most relapses were detected during regular follow-up visits (Fig. 2) and only 8.5% (30 of 353) of relapses were detected on the patients’ initiative independent of the regular follow-up program.

For the 16 patients who relapsed after the 5-yr follow-up program, relapses were detected by radiology only (five patients), radiology and elevation of TMs (nine patients), and two relapses were detected by physical examination. These investigations were performed on patients’ initiatives due to symptoms.

A biopsy at relapse was performed in 271 patients; 92.3% (250 of 271) of the biopsy specimens revealed seminoma and 4.1% (11 of 271) revealed nonseminoma. In 3.7% (10 of 271) of the biopsy specimens, the material was insufficient for a histologic diagnosis. Stage and treatment at relapse are shown in Table 2 and Supplemental Table 1. All relapsing patients belonged to the good prognostic group, according to the International Germ Cell Cancer Collaborative Group [8], apart from two relapses in the intermediate group.

Treatment and outcome of relapse treatment for all patients are shown in Figure 1. Radiotherapy was administered to 230 patients at relapse. A second relapse was observed in 12.6% (29 of 230) of these patients. All but one of the second relapses were located outside the radiation field, and all were treated with BEP.

BEP was administered as initial treatment in 133 relapses and three patients received other chemotherapy than BEP. Eight patients had a second relapse after BEP. Three patients had surgery only for their first relapse. All three later developed a second relapse and were treated with BEP. In total, 8.6% (168 of 1954) of the study population received chemotherapy due to relapse.

Of 16 relapses occurring at >5 yr of follow-up, 12 patients had no evidence of disease, one died of treatment complications (pulmonary edema during chemotherapy) before response evaluation, and three patients died of GCC.

During the study period, 200 patients died. Thirteen patients died of seminoma: eight of progressive disease, and five due to other causes during the study period (Supplemental Table 2).

The OS after 5, 10, and 15 yr was 98.1%, 95.5%, and 91.6%, respectively; and the DSS at 5, 10, and 15 yr was 99.6%, 99.4%, and 99.3%, respectively.

In both reduced multivariate complete cases and imputed models (Table 3), tumor size was a significant independent risk factor for relapse, with hazard ratios (HR) for a 2-fold difference in tumor size of 1.59 (95%
In this large retrospective study of stage I seminoma patients followed on surveillance, we observed 18.1% relapses within 5 yr of follow-up, and 0.8% relapses after 5 yr.

The inclusion of VI+ in this multivariate model showed that the p value in the final model was 0.059 and removing EPI from the model resulted in VI+ being significant (p = 0.022). Table 4 shows 5-yr relapse-free rates for patients with EPI or VI+, based on the imputed reduced models. The results of univariate and unreduced multivariate analyses are listed in Supplemental Table 3.

Incorporating the period 1985 to 1992 as a separate variable in our analysis did not influence the finding of prognostic factors.

A total of 4.7% (91 of 1954) of the patients were lost to follow-up, with 1.8% (35 of 1954) lost before 2 yr of follow-up. Four of these patients developed a relapse; one patient died of disseminated disease (intermediate prognostic group) despite BEP treatment. Two were successfully treated with BEP (good prognostic group) and one with radiotherapy (local relapse in scrotum; good prognostic group). Another 12 patients dropped out of the follow-up program after receiving treatment for a relapse. None of these patients had a second relapse.

4. Discussion

In this large retrospective study of stage I seminoma patients followed on surveillance, we observed 18.1% relapses within 5 yr of follow-up, and 0.8% relapses after 5 yr.

confidence interval [CI], 1.31–1.92; p < 0.0001) and 1.41 (95% CI, 1.22–1.62; p < 0.0001), respectively. Furthermore, the presence of VI+ was independently significant in the complete case model (HR: 1.46; 95% CI, 1.05–2.02; p = 0.026), and although EPI was not significant when included in this model (p = 0.11), removal of VI+ resulted in EPI being independently significant in the multivariate model (HR: 1.57; 95% CI, 1.04–2.38; p = 0.033). An interaction between VI+ and EPI could not be shown (p = 0.69). In the imputed model, EPI was independently significant (HR: 1.60; 95% CI, 1.14–2.23; p = 0.006). The inclusion of VI+ in this multivariate model showed that the p value in the final model was 0.059 and removing EPI from the model resulted in VI+ being significant (HR: 1.41; 95% CI, 1.05–1.89; p = 0.022). Table 4 shows 5-yr relapse-free rates for patients with EPI or VI+, based on the imputed reduced models. The results of univariate and unreduced multivariate analyses are listed in Supplemental Table 3.

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Table 2 – Stage and treatment at relapse

<table>
<thead>
<tr>
<th>Stage at relapse</th>
<th>Radiotherapy</th>
<th>BEP</th>
<th>Surgery only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>103</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Iib</td>
<td>115</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Iic</td>
<td>10</td>
<td>65</td>
<td>1</td>
</tr>
<tr>
<td>Ila</td>
<td>2</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Iib</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>IS</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>230</td>
<td>136</td>
<td>3</td>
</tr>
</tbody>
</table>

Prognostic group

| Good             | 230          | 134 | 3            |
| Intermediate      | 0            | 2   | 0            |

BEP = bleomycin, etoposide, and cisplatin; IS = elevation of serum tumor markers only.
Median time to relapse was 13.7 mo. The 15-yr DSS and OS rates were 99.3% and 91.6%, respectively. The relapse rate and survival at 5 yr in the present study is similar to previously published data [13–17].

Tumor size was the most important risk factor for relapse in our analysis. VI+ and EPI were also identified as prognostic factors for relapse. Their roles were less clear; however, both were statistically significant if the other factor was excluded.

Prognostic factors varied greatly in previous studies and definitions of individual factors differ. In a pooled analysis of prognostic factors by Warde et al. [18], tumor size >4 cm and invasion of rete testis were independent risk factors for relapse. These risk factors have subsequently been included in guidelines [1] and are used in risk-adapted treatment [19]. However, an attempt to validate these risk factors was unsuccessful, as only tumor size remained significantly related to relapse [20]. Rete testis invasion was not significant in our study. Our study confirms tumor size as an important risk factor for relapse.

The presence of EPI and VI+ significantly increased the risk for relapse in the present study. Previous surveillance studies did not test EPI as a prognostic factor [14–17,20]. Randomized studies comparing surveillance with results from adjuvant treatment are lacking. Adjuvant radiotherapy is highly efficient in limiting the number of relapses (<5%) and maintaining high DSS rates [21]. The use of adjuvant carboplatin appears to be as efficient as radiotherapy [22] and surveillance in maintaining DSS. The short-term side effects are minimal; however, long-term follow-up studies with details on late relapses and side effects are still missing. About 5% of the patients treated with adjuvant

![Detection of relapses over time and detection methods of relapses. Clinical examination includes relapses with enlarged lymph nodes and local relapses in the scrotum. Radiology includes relapses detected by computed tomography scans, ultrasound, and x-rays. Relapses occurring >5 yr after orchiectomy were seen at year 6 (one patient), at year 7 (four patients), at year 8 (three patients), at year 10 (four patients), at year 11 (two patients), at year 12 (one patient), and at year 15 (one patient). TM = tumor marker.](image)

![Fig. 3 – Distribution of relapses over time and detection methods of relapses. Clinical examination includes relapses with enlarged lymph nodes and local relapses in the scrotum. Radiology includes relapses detected by computed tomography scans, ultrasound, and x-rays. Relapses occurring >5 yr after orchiectomy were seen at year 6 (one patient), at year 7 (four patients), at year 8 (three patients), at year 10 (four patients), at year 11 (two patients), at year 12 (one patient), and at year 15 (one patient). TM = tumor marker.](image)

Table 3 – Multivariate analyses, complete cases, and imputed results on reduced models

<table>
<thead>
<tr>
<th>Parameter tested</th>
<th>Complete case, reduced model VI+</th>
<th>Complete case, reduced model EPI</th>
<th>Complete case, reduced model VI+</th>
<th>Complete case, reduced model EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI), p value</td>
<td>HR (95% CI), p value</td>
<td>HR (95% CI), p value</td>
<td>HR (95% CI), p value</td>
</tr>
<tr>
<td>Age</td>
<td>0.90 (0.78–1.02), 0.1029</td>
<td>0.88 (0.76–1.01), 0.0636</td>
<td>0.93 (0.85–1.03), 0.1705</td>
<td>0.93 (0.84–1.02), 0.1232</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.59 (1.31–1.92), &lt;0.0001</td>
<td>1.63 (1.34–1.98), &lt;0.0001</td>
<td>1.38 (1.20–1.60), &lt;0.0001</td>
<td>1.41 (1.22–1.62), &lt;0.0001</td>
</tr>
<tr>
<td>VI+</td>
<td>1.46 (1.05–2.02), 0.0257</td>
<td>Not included</td>
<td>1.41 (1.05–1.89), 0.0217</td>
<td>Not included</td>
</tr>
<tr>
<td>EPI</td>
<td>Not included</td>
<td>1.57 (1.04–2.38), 0.0333</td>
<td>Not included</td>
<td>1.60 (1.14–2.23), 0.0064</td>
</tr>
</tbody>
</table>

CI = confidence interval; EPI = invasion of epididymis; HR = hazard ratio; VI+ = vascular invasion.

* Model VI+ includes VI+ but not EPI.

** Model EPI includes invasion of epididymis but not vascular invasion.
carboplatin relapse, mainly in the retroperitoneal lymph nodes, emphasizing the need for continued CT scans for at least some years after adjuvant treatment [23].

The risk of second relapse was higher in relapsing patients treated with radiotherapy compared to patients treated with BEP. This is one of the reasons for limiting radiotherapy to relapses <3 cm.

The follow-up schedule for stage I seminoma patients is controversial. Some guidelines suggest lifelong follow-up, and some recommend 5 or 10 yr of follow-up [21,24,25]. Based on the present data, we propose a 5-yr follow-up program, as suggested in Figure 2. A modest number of relapses (4.3%) were observed beyond 5 yr; three of these patients died of GCC and one of treatment complications, stressing the importance of patient education on relapse symptoms when ending the follow-up. Continuing routine CT scans of all patients to detect this very small number of relapses is of limited value. This will add excessive radiation to all patients in the follow-up program, with a theoretical risk of inducing new cancers [26]. Use of low-dose CT scans has lowered this risk. The ongoing Trial of Imaging and Surveillance in Seminoma Testis [27] comparing a reduced number of CT scans with magnetic resonance scans might add important information for the design of future follow-up programs. The use of abdominal ultrasound is currently not recommended in the follow-up of seminoma patients [2].

It has been argued that TMs add no additional value to CT scans and clinical examinations for detecting relapses [28]. In the present study, raised TM levels were the only sign of relapse in three patients. Increases in TM levels were, however, either the reason for performing a CT scan or accompanying CT scans in detecting relapses in 19.5% of patients relapsing <5 yr. In the very late relapses, more than one-half of the patients showed increased TM levels. Hence, measurement of TM levels should be advocated for previous GCC patients with symptoms of severe disease.

Compliance is essential for a successful surveillance program. Compared to other studies, our noncompliance rate was low: 4.7% of patients dropped out before the end of the 5-yr follow-up. One of these patients died of GCC. Obviously, small population size and outstanding registries facilitate the identification of patients lost to follow-up.

Furthermore, the free health-care services might also attribute to the high compliance. Less optimal health-care systems might compromise compliance.

The retrospective nature of our study adds possible limitations to our results. The number of missing values and patients’ characteristics varied over time. In the later years of the study period, the pathology reports had more details and exact descriptions. Our data reflect the results of surveillance in a population-based setting. We handled the missing values by using multiple imputations in statistical analyses. The 352 patients who received adjuvant radiotherapy during the study period were excluded from our study (Fig. 1). Most of these patients had a tumor >6 cm. This treatment strategy was based on a previous surveillance study in seminoma stage I published by von der Maase et al. in 1993 [16]. Accordingly, the risk of relapse in the present study (Table 4) could have been higher if these patients had been followed with surveillance too.

The major strengths of the present study are the large number of uniformly handled patients, the long follow-up time, and the unique merging of registries, which enabled us to identify all very late relapsing patients and patients lost to follow-up.

5. Conclusions

Virtually all patients with stage I seminoma are cured regardless of the postorchiectomy management. With DSS >99%, stage I seminoma is not a disease conferring a significant risk for death, but the inherent side effects of oncologic treatment can be a risk for the patient. Smaller retrospective studies have evaluated the surveillance strategy and proved it safe, and our study substantiates this. Active surveillance prevents treatment in the vast majority (80%) of patients. The internal validation confirms our finding of risk factors; however, they still need external validation, preferably in a prospective study, before being implemented in a clinical setting and being used for risk-adapted treatment.

Author contributions: Mette Saksø Mortensen 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.
Study concept and design: Mortensen, Lauritsen, Gundgaard, Daugaard, von der Maase.

Acquisition of data: Mortensen, Lauritsen, Gundgaard, Daugaard, von der Maase, Agerbæk, Holm.

Analysis and interpretation of data: Mortensen, Lauritsen, Gundgaard, Daugaard, von der Maase, Christensen.

Drafting of the manuscript: Mortensen, Lauritsen, Gundgaard, Daugaard, von der Maase, Christensen.

Critical revision of the manuscript for important intellectual content: Mortensen, Lauritsen, Gundgaard, Daugaard, von der Maase, Christensen.

Statistical analysis: Mortensen, Lauritsen, Christensen.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.07.001.

References


