Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA)


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Background: The purpose of the protocol was to reduce the treatment burden in clinical stage I (CSI) seminoma by offering risk-adapted treatment. The protocol aimed to prospectively validate the proposed risk factors for relapse, stromal invasion of the rete testis and tumor diameter >4 cm, and to evaluate the efficacy of one course of adjuvant carboplatin.

Patiens and methods: From 2007 to 2010, 897 patients were included in a prospective, population-based, risk-adapted treatment protocol implementing one course of adjuvant carboplatin AUC7 (n = 469) or surveillance (n = 422). In addition, results from 221 patients receiving carboplatin between 2004 and 2007 are reported.

Results: At a median follow-up of 5.6 years, 69 relapses have occurred. Stromal invasion of the rete testis [hazard ratio (HR) 1.9, P = 0.011] and tumor diameter >4 cm (HR 2.7, P < 0.001) were identified as risk factors predicting relapse. In patients without risk factors, the relapse rate (RR) was 4.0% for patients managed by surveillance and 2.2% in patients receiving adjuvant carboplatin. In patients with one or two risk factors, the RR was 15.5% in patients managed by surveillance and 9.3% in patients receiving adjuvant carboplatin. We found no increased RR in patients receiving carboplatin <7 × AUC compared with that in patients receiving ≥7 × AUC.

Conclusion: Stromal invasion in the rete testis and tumor diameter >4 cm are risk factors for relapse in CSI seminoma. Patients without risk factors have a low RR and adjuvant therapy is not justified in these patients. The efficacy of adjuvant carboplatin is relatively low and there is need to explore more effective adjuvant treatment options in patients with high-risk seminoma. The data do not support the concept of a steep dose response for adjuvant carboplatin.

Key words: testicular cancer, seminoma, surveillance, adjuvant carboplatin, risk-adapted, prognostic factors

Introduction

Since 1981 SWENOTECA has developed management protocols and initiated studies for patients with testicular cancer, of which clinical stage I (CSI) seminoma is the most frequent presentation, accounting for 45%–50% of all patients and 85% of patients with seminoma [1]. Treatment options in CSI seminoma have until the last decade been radiotherapy or surveillance. SWENOTECA V (2000–2007) was the first SWENOTECA protocol to include patients with seminoma. Of the 1384 patients included, 1191 (86%) were CSI. Management options were either...
adjuvant radiotherapy or surveillance [2]. During the time frame of SWENOTECA V, important data regarding CSI seminoma were published. A study identifying stromal invasion of the rete testis and tumor diameter >4 cm as independent risk factors for relapse was published in 2002 [3]. Subsequently, results from the MRC-TE19/EORTC30982 trial, randomizing CSI seminoma patients to adjuvant radiotherapy or one course of adjuvant carboplatin [dosed according to area under the dose–time concentration curve ×7 (AUC7)], showed chemotherapy as an equivalent alternative to radiotherapy with respect to efficacy [4]. Moreover, alarming data on excess mortality following radiotherapy in testicular cancer emerged [5, 6]. Consequently, adjuvant radiotherapy was abandoned as a standard treatment option within SWENOTECA, and adjuvant carboplatin was introduced in 2004. A risk-adapted protocol, SWENOTECA VII, was implemented in 2007, aiming to minimize treatment burden by reducing the risk of toxic salvage treatment in patients with a high risk of relapse. We also aimed to prospectively validate stromal invasion of the rete testis and tumor diameter >4 cm as risk factors for relapse. We now report the results of this protocol. To further evaluate the efficacy of one course of adjuvant carboplatin in a real-world setting, we also report long-term follow-up of patients treated with adjuvant carboplatin included and prospectively registered in the SWENOTECA V protocol from 2004.

patients and methods

From 2007 to 2010, a total of 897 men with CSI seminoma were included in SWENOTECA VII that included all eligible patients in Norway and Sweden, except from one Norwegian center. All patients were registered at diagnosis with details regarding treatment and follow-up collected consecutively. The clinical staging procedure consisted of a clinical examination and a computed tomography (CT) of the thorax, abdomen, and pelvis. Tumor markers, α-fetoprotein (AFP), human chorionic gonadotropin β, and lactate dehydrogenase were measured before and after orchiectomy. Patients with normal tumor markers and no lymph nodes with largest transversal diameter exceeding 1 cm were staged as CSI. Only patients with pure seminoma and a normal AFP level were included. Spermatocytic seminomas were excluded.

Risk factors were defined as largest tumor diameter >4 cm and/or stromal invasion of the rete testis. Patients with CSI seminoma with no or one risk factor were recommended surveillance, whereas patients with two risk factors were recommended one course of adjuvant carboplatin AUC7. Regardless of the recommendations, patients were free to choose between adjuvant carboplatin and surveillance following thorough written and oral information regarding the pros and cons of the different modalities. In addition to the patients included in SWENOTECA VII, 221 men treated with adjuvant carboplatin between 2004 and 2007, were included in the analysis. These patients were treated when the SWENOTECA V study was active, and were all prospectively registered and followed according to SWENOTECA V. Adjuvant carboplatin was initially not a treatment option in SWENOTECA V, but data on adjuvant carboplatin became available in the time frame between SWENOTECA V and SWENOTECA VII. Some of these patients have previously been reported, but then with limited follow-up time [2].

To assure the population-based nature of the dataset, data from the National cancer registry in Sweden and in Norway were cross-checked against hospital databases. The Swedish and Norwegian medical ethics committees approved the study.

Table 1. Treatment, follow-up, relapse, and survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N of relapse</th>
<th>Relapse rate (%)</th>
<th>Median follow-up*, IQR (years)</th>
<th>Median time to relapse, range (years)</th>
<th>5-year OS (%), 10-year OS (%)</th>
<th>5-year CSS (%), 10-year CSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>69/1118</td>
<td>6.7</td>
<td>5.6 (4.4–7.0)</td>
<td>1.4 (0.2–6.5)</td>
<td>98.9, 97.8</td>
<td>100, 99.9</td>
</tr>
<tr>
<td>Surveillance</td>
<td>29/422</td>
<td>7.5</td>
<td>5.4 (4.5–6.3)</td>
<td>1.3 (0.4–5.6)</td>
<td>99.2, 96.8</td>
<td>100, 99.6</td>
</tr>
<tr>
<td>Carboplatin AUC7</td>
<td>40/690</td>
<td>6.2</td>
<td>5.7 (4.3–7.3)</td>
<td>1.7 (0.2–6.5)</td>
<td>98.9, 98.5</td>
<td>100, 100</td>
</tr>
<tr>
<td>Other</td>
<td>0/66</td>
<td>3.0</td>
<td>4.3 (3.0–5.7)</td>
<td>n.a.</td>
<td>66.7, 66.7</td>
<td>100, 100</td>
</tr>
</tbody>
</table>

*From orchiectomy to last documented follow-up at hospital.

Table 1 provides a summary of treatment, follow-up, overall survival (OS), and cause-specific survival (CSS). Follow-up was >3 years in 94.8% of patients. Of the 69 patients with relapse, one patient, initially managed with surveillance, died of complications to salvage chemotherapy. All patients with relapse were in the good prognosis group (Table 2). The median follow-up in regard to OS and CSS is 6.6 years. Seventeen patients have died (supplementary Table S1, available at Annals of Oncology online).

follow-up

Clinical examination, tumor markers, chest X-ray, and abdominal/pelvic imaging with CT/magnetic resonance imaging (MRI) were performed every 4 months in years 1 and 2, every 6 months in years 3 and 4 then yearly until year 10.

statistical analysis

Statistical analyses are presented in supplementary material S1, available at Annals of Oncology online.

results

Table 1 provides a summary of treatment, follow-up, overall survival (OS), and cause-specific survival (CSS). Follow-up was >3 years in 94.8% of patients. Of the 69 patients with relapse, one patient, initially managed with surveillance, died of complications to salvage chemotherapy. All patients with relapse were in the good prognosis group (Table 2). The median follow-up in regard to OS and CSS is 6.6 years. Seventeen patients have died (supplementary Table S1, available at Annals of Oncology online).

prognostic factors for relapse

Lymphovascular invasion, stromal invasion of the rete testis, and largest tumor diameter were registered as possible prognostic factors for relapse (supplementary Table S2, available at Annals of Oncology online). In multivariate analyses, both
stromal invasion of rete testis and tumor diameter >4 cm retained statistical significance with a hazard ratio (HR) of 2.7, $P < 0.001$ for tumor diameter >4 cm and an HR of 1.9, $P = 0.011$ for stromal invasion of rete testis (Table 3). An exploratory analysis also found tumor diameter as a continuous variable to be predictive of relapse. Risk factors according to treatment are presented in supplementary Table S3, available at Annals of Oncology online, and relapse rates (RRs) according to risk factors and treatment are presented in supplementary Table S4, available at Annals of Oncology online.

relapses following surveillance

The RR in patients managed by surveillance was 7.5%. There was a significant difference in relapses between patients with no risk factors (4.0%) and those with one or two risk factors (15.5%), $P < 0.001$ (Figure 1). Of the 29 relapses (median time to relapse, 1.3 years), 5 (17%) occurred more than 2 years following orchectomy and 1 (3%) beyond 5 years. The vast majority (96%) had retroperitoneal lymph nodes as the only site of relapse (Table 2). Patients managed by surveillance according to the recommendations (no or one risk factor) had an RR of 7.7%.

relapses following adjuvant carboplatin

The RR in patients receiving adjuvant carboplatin was 6.2%. There was a significant difference in relapses between patients with no risk factors and those with one or two risk factors, with a RR of 2.2% and 9.3%, respectively, $P = 0.001$ (Figure 1). Of the 40 relapses (median time to relapse, 1.7 years), 13 (33%) occurred more than 2 years following orchectomy and 1 (3%) beyond 5 years. Patients receiving adjuvant carboplatin according to the recommendations (two risk factors) had a RR of 10.6%. One patient experienced a second relapse. This patient did complete only two of four planned courses of salvage chemotherapy with etoposide and cisplatin (EP). The subsequent relapse was treated with three courses of paclitaxel, ifosfamide, and cisplatin (TIP) followed by a retroperitoneal lymphnode dissection (necrosis only). The patient is 6 years

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**Table 2.** Relapses details

<table>
<thead>
<tr>
<th>N</th>
<th>Stage* (CS Mk+, CSIIA, CSIIIB, CSIII, CSIV)</th>
<th>Prognostic group (good, intermediate)</th>
<th>Relapse verificationb (MRI/CT, markers, PET–CT, biopsy, symptoms)</th>
<th>Treatment of relapse (chemotherapy, radiotherapy, surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>29 (6, 19, 2, 0, 1) n = 28c</td>
<td>100%, 0</td>
<td>(28, 10, 6, 5, 2) n = 29</td>
<td>(21d, 6, 2d)</td>
</tr>
<tr>
<td>Adjuvant carboplatin</td>
<td>40 (1, 9, 26, 0, 4, 0) n = 40</td>
<td>100%, 0</td>
<td>(39, 8, 11, 11, 1) n = 40</td>
<td>(35e, 3, 2e)</td>
</tr>
</tbody>
</table>

*Stage according to modified Royal Marsden.
bMay be multiple modalities of relapse verification.
cOne patient diagnosed with relapse during emigration. Missing data regarding exact stage.
 dEP × 4, n = 12, BEP × 3, n = 5, BEP × 4, n = 1, EP × 1, n = 1 (died during salvage therapy), carboplatin, etoposide, bleomycin (CEB) × 4, n = 1.
 eOne patient received radiotherapy following primary surgery.
 fEP × 4, n = 1, BEP × 3, n = 5, BEP × 4, n = 3, CE × 3, n = 1, EP × 2, n = 1 (did not show up for third course of chemotherapy. Subsequent second relapse treated with TIP × 3 and surgery).
 gOne patient received radiotherapy following primary surgery.

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**Table 3.** Cox proportional hazards survival regression for relapse in CSI seminoma, stratified by treatmenta

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariable analysis</th>
<th>Multivariable analysisb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N of patients HR 95% CI</td>
<td>N of patients HR 95% CI</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 cm</td>
<td>696 (63%) 1.0 1.0–5.1</td>
<td>635 (1.0 1.0–5.1)</td>
</tr>
<tr>
<td>&gt;4 cm</td>
<td>414 (37%) 3.1 1.8–5.1</td>
<td>362 (2.7 1.6–4.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Invasion rete testis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>726 (65%) 1.0 1.0–3.7</td>
<td>726 (1.0 1.0–3.7)</td>
</tr>
<tr>
<td>Present</td>
<td>273 (25%) 2.2 1.4–3.7</td>
<td>271 (1.9 1.2–3.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>113 (10%)</td>
<td></td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>639 (57%) 1.0 1.0–3.7</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>278 (25%) 1.5 0.9–2.7</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>195 (18%)</td>
<td></td>
</tr>
</tbody>
</table>

aPatients treated with one course of adjuvant carboplatin or surveillance (n = 1112).
bSurveillance: 29 events, 366 patients censored; carboplatin: 38 events, 564 patients censored, 115 cases with missing values.
after salvage treatment without evidence of disease. Most patients (90%) had abdomen as only site of relapse (Table 2). If the dose was calculated according to AUC7, with no more than 50 mg adjusted downward. Detailed data on dosing were available for 629/690 patients. Overall, 164/629 (26%) of patients received a dose of <AUC7 the median dose being 85% of the recommended dose. The predominant reason for receiving a dose of <AUC7 was the use of a GFR corrected for body surface area instead of an uncorrected GFR. The RR in patients with correct and lower than recommended dose was 7.1% and 6.8%, respectively, P = 0.947 (Figure 1).

discussion

We present the largest risk-adapted study in CSI seminoma, with the largest cohort of patients treated with one course of adjuvant carboplatin. It shows the feasibility of a risk-adapted approach in CSI seminoma implementing patient autonomy in a large patient population. No patients died from progressive seminoma and only one patient died of treatment-related toxicity. The study is prospective and population-based and should thereby reflect what is to be expected in a real-world setting, giving the data high external validity.

Although the protocol advocated patient autonomy, recommendations were stratified according to risk factors. Only patients with two risk factors were recommended adjuvant carboplatin. Within the risk-adapted SWENOTECA VII protocol, 11.2% of the men had two risk factors, but in all 53% of the patients chose adjuvant carboplatin. Patients were informed of an estimated RR of 15% if no or one risk factor was present. This indicates that many well-informed patients may prefer adjuvant treatment even if the absolute risk of relapse is low. The proportion of patients choosing adjuvant carboplatin differed between hospitals, probable due to the physician bias regarding treatment options.

We confirmed both tumor diameter >4 cm and stromal invasion of rete testis as independent risk factors for relapse with HRs comparable with the initial publication by Warde et al. [3]. Few patients had two risk factors, and the majority, 137/149, received adjuvant carboplatin. The number of relapses was low and it was not possible to estimate an accurate HR for patients with two risk factors only. Consequently, patients were grouped according to no or any risk factor present. Tumor diameter, both with a cutoff of >4 cm, >3 cm, and as a continuous variable, has been reported to be a risk factor for relapse in several recent patients series [8–10]. The results from a previous seminoma protocol, SWENOTECA V, did not identify tumor diameter as a prognostic factor. However, no data regarding invasion of the rete testis were recorded in that study [2]. The HR for relapse is lower for stromal invasion than for tumor diameter >4 cm. Thus, as relapses are few, more patients are needed to verify stromal invasion of the rete testis as a prognostic factor. The authors of the study by Warde et al. performed a retrospective validation study confirming tumor size as a prognostic factor, however, no data regarding invasion of the rete testis were recorded in that study [2]. The HR for relapse is lower for stromal invasion than for tumor diameter >4 cm. Thus, as relapses are few, more patients are needed to verify stromal invasion of the rete testis as a prognostic factor. The authors of the study by Warde et al. performed a retrospective validation study confirming tumor size as a prognostic factor, however, no data regarding invasion of the rete testis were recorded in that study [2]. The HR for relapse is lower for stromal invasion than for tumor diameter >4 cm.
publications regarding proposed risk factors in seminoma, and perhaps a reason why results concerning stromal invasion of the rete testis as a prognostic factor have varied. Several of the recent studies on adjuvant chemotherapy reported few relapses rendering the identification of risk factors difficult. Other studies used old, retrospective, and incomplete datasets, making interpretation of the results difficult [12].

Patients with one risk factor were recommended surveillance, but could choose adjuvant carboplatin. The tumor diameter was larger in patients with one to two risk factors receiving adjuvant carboplatin versus in patients with one to two risk factors undergoing surveillance (median 55 versus 45 mm). As tumor diameter as a continuous variable was found to be a prognostic factor, a small selection bias can therefore not be ruled out. Tumor diameter did not differ between patients with no risk factors receiving adjuvant carboplatin and those managed by surveillance, as illustrated in supplementary Table S3.

The RR after adjuvant carboplatin in this study was 6.2% and 5.3% in the MRC TE19/EORTC30982 [13]. The numerically higher RR is probably a result of more patients with risk factors receiving adjuvant carboplatin.

In an exploratory analysis, the authors of the MRC TE19 study found a nonsignificant increased risk of relapse in patients receiving a dose of carboplatin <AUC7. They compared patients being dosed using radioisotope GFR estimation with patients in whom urinary creatinine clearance was used, the latter were recommended to receive a 90% dose and hence defined as receiving carboplatin <AUC7. The recommendation was based on the assumption that 24-h urinary creatinine clearance overestimates the true GFR. The mean GFR obtained in the MRC TE19 was similar between the groups, and the authors concluded that the 90% dose adjustment was inappropriate [14]. The analysis regarding dose intensity and risk of relapse in the MRC TE19 study may more likely be a comparison between hospitals using different modalities of GFR estimation than a true comparison of dose intensity. In our study, many patients received a lower dose than recommended, mostly because the carboplatin dose was calculated from a corrected GFR. Although this resulted in a median dose reduction of 15%, the RR was not increased. Hence, our data do not indicate a steep dose–response effect when using one course of adjuvant carboplatin AUC7.

The low RR in patients without risk factors is in accordance with reports from the Spanish Germ Cell Cancer Group [8, 15], and with an estimated risk of relapse below 5% adjuvant therapy may not be justified.

Adjuvant carboplatin is an established treatment option in CSI seminoma. Although well tolerated and easily administered, the efficacy of one course of adjuvant carboplatin is disappointing. Almost one in 10 carboplatin-treated patients with risk factors will experience relapse, and the estimated number needed to treat (NNT) to prevent one relapse is 15–20.

In CSI nonseminoma, one course of adjuvant bleomycin, etoposide, and cisplatin (BEP), reduces the risk of relapse by 90%–95% [16]. In high-risk CSI nonseminoma, the NNT to prevent one relapse is 2 and, even in low-risk nonseminoma, the NNT of 7–8 is lower than in CSI seminoma treated with adjuvant carboplatin. There is clearly a need for more effective adjuvant therapy in CSI seminoma. Two courses of carboplatin are shown to give a lower RR in patients with risk factors [8]. The efficacy of one course of adjuvant BEP has not been explored in CSI seminoma. Given the high chemosensitivity of seminomas, a very low RR is expected, and one adjuvant BEP cycle is assumed to result in a minimum 90%–95% reduction of relapse rate. In the ongoing SWENOTECA ABC-study, men with CSI seminoma and at least one risk factor are randomized to either one course of carboplatin AUC7 or one BEP.

The data confirm surveillance as a good option for all patients with CSI seminoma.

SWENOTECA has the same follow-up schedule for surveillance and adjuvant carboplatin. All relapses were diagnosed in early stages, mainly by imaging, and all were classified as good prognosis. The current recommendation is 10 years of follow-up with clinical examination, tumor markers, and abdominal/pelvic MRI performed every 6 months, years 1 and 2 and annually year 3–6, and at years 8 and 10 (www.swenoteca.org).

In conclusion, tumor diameter >4 cm and stromal invasion of the rete testis are independent risk factors for relapse in CSI seminoma. A risk-adapted management strategy in CSI seminoma is feasible, reducing the number of patients in need of salvage therapy. There is a need to explore more efficient adjuvant treatment options in patients with high-risk seminoma, and to develop novel models to more accurately predict patients with a high risk of relapse.

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**disclosure**

The authors have declared no conflicts of interest.

**references**


Safety and clinical activity of vascular endothelial growth factor receptor (VEGFR)–tyrosine kinase inhibitors after programmed cell death 1 inhibitor treatment in patients with metastatic clear cell renal cell carcinoma

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Background: Emerging agents blocking the programmed cell death 1 (PD-1) pathway show activity in metastatic clear cell renal cell carcinoma (mRCC). The aim of this study was to evaluate the efficacy and safety of vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR)–tyrosine kinase inhibitor (TKI) therapy after PD-1 inhibition.

Patients and methods: Patients with mRCC treated with anti-PD-1 antibody (aPD-1) monotherapy or in combination (with VEGFR-TKI or ipilimumab) that subsequently received VEGFR-TKI were retrospectively reviewed. The efficacy end points were objective response rate (ORR) and progression-free survival (PFS) stratified by the type of prior PD-1 regimen. Safety by the type and PD-1 exposure was also evaluated.