MANAGEMENT OF PATIENTS WITH CLINICAL STAGE I NONSEMINOMATOUS TESTICULAR GERM CELL TUMOURS: ACTIVE SURVEILLANCE VERSUS PRIMARY CHEMOTHERAPY VERSUS NERVE SPARING RETROPERITONEAL LYMPHADENECTOMY

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Summary.- Clinical stage I testicular nonseminomatous germ cell tumours (NSGCT) are highly curable. Following orchidectomy a risk-adapted approach using active surveillance (AS), nerve sparing retroperitoneal lymph node dissection (nsRPLND) and primary chemotherapy is recommended by the current guidelines.

CS I is defined negative or declining tumour markers to their half-life following orchidectomy and negative imaging studies of the chest, abdomen and retroperitoneum. Low risk CS I NSGCT are defined by the absence of vascular invasion, low percentage of embryonal carcinoma (ECA) and low proliferating Ki-67 index. High risk CS I NSGCT are defined by the presence of VI, high percentage of ECA and a high Ki-67 index.

According to the current guidelines, active surveillance, primary chemotherapy and nerve sparing RPLND represent 3 treatment options with the same high cure rate of about 100% but significantly different long-term complications. As demonstrated, active surveillance can be performed in low risk and in high risk NSGCT with an anticipated relapse rate of about 15% and 50%. The majority of patients will relapse with good and intermediate prognosis tumours which have to be treated with 3 to 4 cycles chemotherapy. About 25% to 30% of these patients will have to undergo postchemotherapy RPLND for residual masses. Primary chemotherapy with 1-2 cycles PEB is a therapeutic option for high risk clinical stage I NSGCT associated with a recurrence rate of only 2-3% and a minimal acute and long-term toxicity rate. Nerve sparing RPLND, if performed properly, will cure about 85% of all high risk patients with clinical stage I NSGCT without the need for chemotherapy.

Although armchair calculations of the odds of cure and toxicity associated with the various treatment options can be performed, recommendations about the most optimal therapy in clinical stage I NSGCT remain controversial. There seems to be a consensus that active surveillance is the treatment strategy of choice for CS I low risk patients. However, there is no clear cut recommendation in high risk patients. Each treatment has its own advantages and disadvantages which have to be discussed thoroughly with the patient. If, however, the positive results of 1 cycle of PEB can be validated, it will become the standard cytotoxic approach for clinical stage I NSGCT.

Keywords: Nonseminoma. Nonseminomatous germ cell tumour. Active surveillance. Retroperitoneal lymph node dissection. Retroperitoneal lymphadenectomy. PEB. Adjuvant chemotherapy. Clinical stage I.
Resumen.- Los tumores testiculares de células germíneas no seminomatosas (TTCGNS) son altamente curables. Después de la orquiectomía las guías clínicas actuales recomiendan un abordaje adaptado al riesgo utilizando vigilancia activa (VA), linfadenectomía retroperitoneal (LRP) con preservación de nervios y la quimioterapia primaria.

El estadio I se define como marcadores negativos o en descenso conforme a su vida media después de la orquiectomía y estudios de imagen del tórax, abdomen y retroperitoneo negativos. Los TTCGNS estadio clínico I de bajo riesgo se definen por la ausencia de invasión vascular, porcentaje de carcinoma embrionario bajo e índice de proliferación Ki-67 bajo. Los TTCGNS estadio clínico I de alto riesgo se definen por la presencia de invasión vascular, alto porcentaje de carcinoma embrionario e índice Ki-67 alto.

De acuerdo con las guías clínicas actuales la vigilancia activa, la quimioterapia primaria y la LRP con preservación nerviosa representan 3 opciones de tratamiento con las mismas altas tasas de curación del 100% aunque con complicaciones a largo plazo significativamente diferentes. Cómo se ha demostrado, se puede hacer vigilancia activa en TTCGNS de bajo y alto riesgo con una tasa de recurrencias anticipada de cerca del 15% y del 50%. La mayoría de los pacientes con tumores de pronóstico bueno e intermedio que recurren tendrán que ser tratados con quimioterapia de 3 a 4 ciclos. Sobre el 25% al 30% de estos pacientes tendrán que someterse a LRP postquirúrgico por masas residuales. La quimioterapia primaria con 1-2 ciclos de BEP es una opción terapéutica para tumores testiculares germinales no seminomatosos en estadío clínico I de alto riesgo, asociada con una tasa de recurrencia de sólo el 2-3% y con una tasa mínima de toxicidad aguda y a largo plazo. La LRP con preservación nerviosa, si se realiza de forma apropiada, curará alrededor del 85% de todos los pacientes de alto riesgo con tumores testiculares germinales no seminomatosos sin necesidad de quimioterapia.

Aunque se puede realizar el cálculo teórico de las probabilidades de cura y de toxicidad asociadas con las diferentes opciones de tratamiento, las recomendaciones sobre el tratamiento más óptimo de los TTCGNS estádio I sigue en controversia. Parece existir un consenso de que la vigilancia activa es la estrategia de tratamiento de elección en pacientes en estadío clínico I de bajo riesgo. Sin embargo, no existen recomendaciones claras en pacientes de alto riesgo. Cada tratamiento tiene sus propias ventajas y desventajas las cuales han de evaluarse.

INTRODUCTION

The majority of patients with nonseminomatous germ cell tumours present with stage I disease (1). The standard treatment options of patients with clinical stage I disease remains controversial since patients have an excellent survival with retroperitoneal lymph node dissection (RPLND), active surveillance or primary chemotherapy. The controversy remained over the last 2 decades since about 30% of all patients will harbour occult microscopic retroperitoneal lymph node metastases which cannot reliably detected by modern imaging studies, tumour markers or molecular approaches. With RPLND the staging reliability is most accurate, however, about 70% are operated unnecessarily and 10% will develop systemic metastases with need for salvage chemotherapy. With primary chemotherapy approximately, 50% to 70% of the patients are overtreated and might be exposed to unnecessary long-term complications. Active surveillance on the other hand is clearly indicated in low risk disease with a recurrence rate of only 15%. In patients with high risk disease the relapse rate varies between 35% and 55% and makes intensive salvage chemotherapy necessary.

It is the aim of the current manuscript to critically review the current recommendations with regard to the most optimal treatment in clinical stage nonseminomatous germ cell tumours (NSGCT).

Definition

Clinical stage I is defined by negative imaging studies of the chest, the abdomen and the small pelvis. Furthermore, in order to verify clinical stage I disease elevated markers should be followed postorchiectomy until normalization. Patients without marker normalization or those in whom markers do not decline according to their half life after orchidectomy do not have stage I disease.

Staging procedures

Recommendations concerning staging investigation are frequently based on low-level evidence rather than on the results of prospective phase III studies.

Computerized tomography (CT) of the chest, abdomen and pelvis are required as initial staging investigations with the mandatory application of oral. and intravenous contrast media (2, 3). For the evaluation of the lung and mediastinum, chest CT scan is more sensitive than plain X-ray films (4, 5).

However, it should be noted that pulmonary/pleural nodules of <1 cm can represent a false positive finding in CT scans (5). Furthermore, CT scans of the abdomen and pelvis might give false-negative results in up to 30% of cases due to difficulties in the interpretation of lymph nodes based on morphology and size alone (2). Therefore, the differentiation between clinical stages I and IIA might be unreliable. A detailed description of the location, number and size of lymph nodes should be provided in the radiology report. Magnetic resonance tomography (MRT) scans of the abdomen and pelvis do not provide additional information and should be restricted to patients to whom intravenous contrast media cannot be given [6]. Based on available data, PET has not conclusively demonstrated to improve sensitivity over staging by doing CT scanning alone (7, 8). Not even in high risk stage I patients PET was sensitive enough to predict early metastatic disease in a statistically significant proportion of patients. In the prospective trial TE22 of the MRC 111 high risk CS I NSGCT underwent 18FDG – PET/CT within 8 weeks after orchiectomy of whom 88 (79%) and 23 (21%) were PET-negative and PET – positive, respectively (8). 87 PET-negative patients proceeded to active surveillance and within a median follow-up of 12 months 33 (37.9%) relapsed. Since the relapse rate among PET-negative patients is fairly high, it can be concluded that 18FDG-PET/CT scanning is not sensitive to identify patients at low risk of relapse among clinical stage I NSGCT. PET scans are not recommended outside clinical trials as part of routine initial staging procedures.

Prognostic Risk Factors

Infiltration of venous blood vessels or lymphatic infiltration (vascular invasion, VI) by the primary tumour are the most important prognostic indicators for occult metastases and must be assessed in all patients (9-13). Without adjuvant treatment 48% of the patients with VI will develop metastases while only 14.22% of those without will relapse (EBM IIIB: 67). Based on these data, VI alone does not represent a valuable prognostic risk factor for a risk adapted approach since it will result in an unnecessary overtreatment rate of about 50%. The proliferation rate as well as the percentage of embryonal carcinoma in relation to the total tumour volume, are further prognostic indicators (11, 12). The combination of absence of VI and a percentage of embryonal carcinoma <45% correctly identified 91.5% of all patients with true pathological stage I disease (11). On the other hand, the presence of VI and a percentage of embryonal carcinoma > 80% correctly predicted pathological stage IIA/B disease in 88% of the patients. Based on these data, the German Testicular Cancer Study Group performed a prospective study in which 200 patients with clinical stage I NSGCT were assigned to RPLND and risk factors were assessed prospectively (12). The combination of absence of VI, percentage of embryonal carcinoma < 50% and a MIB-1 proliferating index < 20% correctly identified pathological stage II disease with an 86.5% accuracy. If none of the prognostic risk factors was present, the risk of occult retroperitoneal disease was 16% and patients were classified as low risk. The risk of lymph node metastases was 65% if at least VI and percentage embryonal carcinoma > 50% were present and the patients were classified high risk. In another small prospective evaluation, Perotti et al. (13) tested a prediction model in which patients with a percentage of embryonal carcinoma > 80% and/or the presence of VI were assigned to a high risk of occult metastatic disease. The authors correctly predicted final pathological stage II disease in 67% when only 1 prognostic factor was present.

The combination of imaging studies, pathohistological evaluation and immunhistochemical staining might improve the prediction of the final pathological stage of the disease. Localization and size of lymph nodes in conjunction with a low volume of embryonal carcinoma, absence of vascular invasion and a low MIB-1 proliferation rate might give important information with regard to the probability of lymph node metastases. In a retrospective analysis of 91 clinical stage I NSGCT who underwent nervesparing RPLND, 40 out of 41 patients were correctly classified as low risk tumours for metastases (14, 15). Patients with lymph nodes < 1cm diameter which are located in the primary landing zone, a low volume of embryonal carcinoma harbour a risk of < 10% of occult retroperitoneal lymph node metastases and might be best managed by active surveillance.

Treatment of patients with non-seminoma CS I

If treatment is performed correctly, the cure rate of patients with CS I NSGCT should be 99% regardless of the management chosen. Basically, three treatment options with the same high cure rate but significantly differences in frequency and type of treatment-associated toxicities might be offered to the patient: active surveillance, primary chemotherapy with 1-2 cycles PEB and nervesparing RPLND. When choosing a risk – adapted approach in clinical stage I NSGCT one has to reflect that all of the patients will be long-term survivors so that long-term side effects of treatment should be minimal or non existent. Therefore, it is the aim of ongoing research to minimize treatment and toxicities without comprising therapeutic efficacy. According to the most recommendations of
the European Germ Cell Cancer Consensus Group Conference (EGCCCG) low risk patients should be primarily offered active surveillance (16), whereas systemic chemotherapy with 2 cycles PEB represents the treatment of choice for high risk patients. Reflecting the published new data, both therapeutic approaches might be challenged.

Active Surveillance

Active surveillance represents a treatment strategy with the aim to detect retroperitoneal or systemic relapses and to treat only those patients with documented metastatic disease thereby decreasing the risk of unnecessary overtreatment.

During the initial post-treatment phase follow-up consists of regular clinical examinations, monitoring of serum tumour markers and imaging investigations. The frequency and type of examinations are dependent on the estimated risk of relapse and the time that has elapsed since completion of therapy and should be modified according to these risks. However, only limited information about the optimal follow-up strategy exists, and at the present time recommendations can only be given for stage I testicular cancer.

When recommending active surveillance for low risk or in certain scenarios also for stage I high risk NSGCT, two major important aspects have to be considered: (1) risk of secondary malignancies due to the repetitive radiation exposure of the imaging studies and (2) more intensive treatment in case of relapse (3 cycles PEB ± postchemotherapy RPLND) as compared to primary active therapy (1 cycle PEB).

In the case of active surveillance for CS I, low risk NSGCT, the relapse rate is 27-30% when considering a long-term follow up of ≤20 years (17, 18). Relapses occur in the retroperitoneum in 54-78% of patients, in the lung in 13-31%, but are very rarely found in more than one visceral organ (1). With this approach 78–86% of patients do not need any further treatment after orchiectomy (10, 12, 17-20). If a patient under surveillance relapses, the administration of chemotherapy will result in a cure rate close to 100%. Only in circumstances not suitable for surveillance is adjuvant chemotherapy with two cycles of BEP recommended. Nerve sparing retroperitoneal lymph node dissection (RPLND) is an option at high-volume expert centers (12). A randomized phase III trial of one cycle BEP versus RPLND in 382 unstratified patients with clinical stage I disease (plus adjuvant chemotherapy for those who were to be pathological stage II after RPLND) suggested a significantly reduced recurrence rate using adjuvant BEP as compared to surgery (1,1% versus 7,5%, respectively (12).

Patients with a low risk of relapse (no VI) should be managed by surveillance according to the EGCCCG recommendations for follow-up, which require at least 5 CT scans performed at 0, 3, 12, 18 and 24 months (16). This follow-up protocol with extensive imaging studies, however, might lead to a high radiation exposure with significant long-term consequences for the patients.

In a recent study Tarin et al. (21) estimated the risk of secondary cancer associated with imaging related radiation during surveillance of stage I NSGCT using computed tomography (CT). In their analysis they evaluated surveillance protocols recommending about 16 CT scans over a 5-year period and they took into consideration a 64-slice CT scanner obtaining images of the abdomen and pelvis with and without the chest. For calculation of organ specific radiation doses a standardized, phantom male patient was used using the Monte Carlo simulation techniques. Lifetime attributable risks of cancer were estimated using the approach outlined in the Biological Effects of Ionizing Radiation VII Phase 2 report (22). With a 5-year surveillance protocol the lifetime cancer risk ranged from 1 in 52 (1.9%) for an 18-year old to 1 in 63 (1.2%) for a 40-year old patient. If chest CTs were also obtained the risk increases to 1 in 39 (2.6%) and 1 in 58 (1.6%), respectively. The relative risk of a secondary malignancy with surveillance compared to a single scan after RPLND is approximately 15.2.

Various studies have been designed to reduce the number of CT scans during the surveillance strategy (23, 24). Atsü et al. (23) analysed the outcome of 140 CS I NSGCT who were followed with only 2 CT scans at postoperative months 6 and 12 with no CT scans thereafter. All patients underwent serial measurements of the serum tumour markers, abdominal ultrasonography and chest X-rays at variable frequency depending on the time intervals between orchidectomy and follow-up. Relapses developed in 32 (24%) patients and they were detected within a median of 5 [2-23] months. 28 relapses developed during the first year and only 4 relapses occurred during the second year of surveillance. All patients were salvaged by systemic chemotherapy combined with postchemotherapy RPLND in 7 cases. In their study, the presence of any embryonal carcinoma in the orchidectomy specimen resulted in a 3.7-fold increase at the relapse risk. In order to reduce the number of CT scans during follow-up, the prospective randomized Medical research Council Trial TE08 was initiated which compared
of patients who relapse with intermediate and poor prognosis disease at relapse (24). 247 patients and 167 patients were randomized to the two-scan and the five-scan group, respectively. Besides CT scans all patients underwent follow-up assessments at various time intervals: clinical examination, evaluation of serum tumour markers AFP, β-hCG and LDH as well as chest X-ray. With a median follow-up of 40 months, 37 (15%) relapses have developed in the two-scan and 33 (20%) relapses have occurred in the five-scan group. None of the patients had poor prognosis disease at time of relapse, but 2 (0.8%) patients and 1 (0.6%) patient had intermediate prognosis disease. There were, however, some other statistically significant differences between the two groups with regard to the indicators of relapse. The proportion of patients in whom elevated tumour markers were the first indicators of relapsing disease was 21.6% and 61.1% in the two-scan and the five-scan group, respectively. Interestingly, 16 patients had normal markers at time of orchidectomy but elevated markers at time of relapse underlining the importance of serum tumour markers measurements in every patient with CS I NSGCT who undergoes active surveillance. In the two arms combined a total of 11 patients developed lung metastases of whom 7 were tumour marker negative. The following conclusions can be drawn from this large prospective randomized trial: (1) fewer CT scans reduce the radiation exposure and costs without harming the patient, (2) regular measurements of β-hCG, AFP and LDH together with chest X-rays and two abdominal CT scans are necessary for a surveillance program, and (3) it is unclear if this approach of reduced imaging studies can be applied for high risk patients since only 10% of the recruited NSGCT demonstrated vascular invasion with a relapse rate of 32%.

Vascular invasion (VI) of the primary tumour is the most important prognostic indicator for relapse. Patients with VI have a 48% risk of developing metastatic disease (10-13, 17-20) whereas only 14-22% of patients without VI will relapse (10, 17-20). A risk adapted strategy based on the presence of VI with the application of 2 cycles PEB chemotherapy is the recommended standard procedure according to the EGCCCG and the EAU guidelines although an overtreatment rate of 52% results due to this fairly insensitive marker (16, ). In this scenario, Kakiashvili et al. (26) reported on the largest experience of nonrisk adapted surveillance in 371 patients with clinical stage I NSGCT. With regard to outcome measurements, patients were stratified into two cohorts based on the time of diagnosis with group 1 being diagnosed between 1981 and 1992 and group 2 being diagnosed between 1993 - 2005. The median follow-up is 6.3 years and the median time to relapse is 7.1 months. Presence of vascular invasion and pure embryonal carcinoma were identified as independent predictors of relapse in both cohorts. 42% and 27.6% of both cohorts were high risk patients and 54.5% and 49.2% of those patients relapsed as compared to only 18.7% and 14.2% in the low risk group. Interestingly, the number of high risk patients decreased over time which might be a result of improved diagnostic modalities and a more precise definition of high risk disease. This nonrisk adapted surveillance strategy resulted in a 5-year disease specific and overall survival rate of 99.2% and 98.2%, respectively. This approach will spare unnecessary treatment in 50% of high risk patients and it will thereby reduce the overall treatment burden in these young men. The retroperitoneum was the relapsing site in 75% of the patients, in another 10% of the patients relapse was only diagnosed by a tumour marker rise.

In another retrospective study, 223 clinical stage I NSGCT underwent surveillance independent on their prognostic risk profile (27). Vascular invasion was present, absent or unknown in 66%, 27%, and 7%, respectively. After a median follow-up, 59 (26%) patients relapsed with good prognosis disease and all were salvaged by systemic chemotherapy, 8% of the patients needed to undergo postchemotherapy RPLND. Only half of the relapsing patients demonstrated vascular invasion in their orchiectomy specimen.

Furthermore, recent studies have questioned the high recurrence rate of close to 50%. In the retrospective study from Divrik et al. (28) the relapse rate was only 35.9% in CS I NSGCT with only 1 risk factor which was defined as either presence of vascular invasion or percentage of embryonal carcinoma > 50%. Rustin et a. (24) reported a 32% 2-year relapse rate among patients with vascular invasion. Also, Stephenson et al. (29) described a progression rate of only 33% in patients with CS I NSGCT who would undergo surveillance based on their studies on primary nerve sparing RPLND. Based on these findings some authors offered surveillance even to patients with high risk CS I NSGCT (26, 27) with excellent outcome. Al-Thourah et al. (30) retrospectively evaluated 107 CS I patients with predominant embryonal carcinoma who underwent active surveillance or nerve sparing RPLND. With a median follow-up of 4 years 33% in the surveillance group experienced relapse and were salvaged with chemotherapy and postchemotherapy RPLND. In the RPLND group 18 (56%) patients had pathological stage I and 14 (44%) had pathological stage II disease. 4 patients experienced a systemic relapse outside the boundaries of resection and all
TABLE 1. Therapeutic burden associated with the different treatment strategies considering the relapse rates given in the most recent series with risk-adapted management calculated per 100 patients; *25/33 pts are pN1 with no need for adjuvant CHT; 8/33 pts are pN2 with the need for 2 cycles of adjuvant CHT; high risk\(^a\) = standard approach with 2 cycles PEB; high risk\(^b\) = minimized approach with 1 cycle PEB. Active surveillance has the lowest therapeutic burden for low risk patients; active surveillance and primary CHT according to the standard have the highest therapeutic burden for high risk patients.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Path. Stage</th>
<th>Relapse</th>
<th>IGCCC</th>
<th>CHT</th>
<th>Total # cycles</th>
<th>RPLND/pt</th>
<th>CHT/pt</th>
<th>Interventions/pt</th>
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<tbody>
<tr>
<td><strong>Surveillance</strong></td>
<td></td>
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<tr>
<td>Low risk</td>
<td></td>
<td>14%</td>
<td>12 good</td>
<td>12 x 3</td>
<td>44</td>
<td>0,04</td>
<td>0,44</td>
<td>0,48</td>
</tr>
<tr>
<td>High Risk</td>
<td></td>
<td>53%</td>
<td>45 good</td>
<td>45 x 3</td>
<td>167</td>
<td>0,14</td>
<td>1,67</td>
<td>1,81</td>
</tr>
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<td><strong>nsRPLND</strong></td>
<td></td>
<td></td>
<td>8 good</td>
<td>8 x 3</td>
<td>24</td>
<td>1,0</td>
<td>0,24</td>
<td>1,24</td>
</tr>
<tr>
<td>Low Risk</td>
<td>PSII = 72%</td>
<td>3%</td>
<td>3 good</td>
<td>3 x 3</td>
<td>31</td>
<td>1,0</td>
<td>0,31</td>
<td>1,31</td>
</tr>
<tr>
<td>High Risk</td>
<td>PSII = 28%</td>
<td>8%</td>
<td>8 good</td>
<td>8 x 3</td>
<td>24</td>
<td>1,0</td>
<td>0,24</td>
<td>1,24</td>
</tr>
<tr>
<td><strong>Primary CHT</strong></td>
<td></td>
<td>1.5%</td>
<td>2 good</td>
<td>100 x 2</td>
<td>206</td>
<td>0,01</td>
<td>2,06</td>
<td>2,07</td>
</tr>
<tr>
<td>High Risk(^a)</td>
<td></td>
<td>3,2%</td>
<td>3 good</td>
<td>100 x 1</td>
<td>109</td>
<td>0,02</td>
<td>1,09</td>
<td>1,11</td>
</tr>
</tbody>
</table>

Primary Chemotherapy

According to the EECGG and the ALA guidelines, patients with a high risk of relapse (VI present) should receive adjuvant chemotherapy with two cycles of adjuvant PEB chemotherapy (16, 25). The application of other cytotoxic regimes such as cisplatin, vinblastine, and bleomycin is oncologically ineffective but is associated with unacceptable toxicity and does not play any role in the adjuvant management of clinical stage II NSGCT. The application of two cycles adjuvant chemotherapy is shown to increase the overall cure rate of 95% and does not play any role in the adjuvant management of clinical stage I NSGCT. By the recommended approach of two cycles adjuvant chemotherapy, 97% of patients will remain relapse-free and 99% of the overall cure rates decreases from 35 to 45%.

Based on these findings, active surveillance might be used in both low and high risk clinical stage NSGCT.

Active surveillance might be used with 65% of patients with a low risk of relapse. Active surveillance might be used with 65% of patients with a low risk of relapse. Active surveillance might be used with 65% of patients with a low risk of relapse. Active surveillance might be used with 65% of patients with a low risk of relapse.
harbourd vascular invasion invasion of the tunica vaginalis, spermatic cord rete testis or the scrotal wall, embryonal carcinoma > 50% (33). With a median follow-up of 79 months, one patient experienced a systemic relapse and another patient developed a contralateral testicular germ cell tumour underlining the high therapeutic efficacy of 2 cycles PEB.

The disadvantage of adjuvant treatment in high-risk patients is that half of the patients who receive adjuvant BEP would not have required chemotherapy at all and may be unnecessarily exposed to the side-effects of chemotherapy (34-38), a possible transient decrease in fertility (39) and possibly a small risk of secondary malignancies, as reported from patients receiving higher doses of chemotherapy (40).

In order to decrease the potential long-term side effects associated with adjuvant chemotherapy, various groups have applied only 1 cycle of PEB chemotherapy in high risk CSI NSGCT (41, 42). In one of the first studies, Gilbert et al. (41) treated 22 CSI NSGCT patients with 1 cycle of the PEB regime. After a median follow-up of 10.2 years, none of the patients relapsed. In another prospective study, Westermann et al. (42) delivered 1 cycle PEB to a cohort of 44 high risk patients, recently the long-term results after a median follow-up of 99 months were reported. 40 patients could be evaluated with 35 (87.5%) patients remaining disease-free and 5 patients who developed a relapse. 2 relapses were located in the contralateral testis and those are not attributable to the high risk NSGCT, so that the true relapse rate is only 7.5%. In a prospective randomized clinical phase-III trial the German Testicular Cancer Study Group (GTCSG) randomized 382 patients with CSI NSGCT to either receive 1 cycle of PEB chemotherapy or RPLND (43). After a median follow-up of 4.7 years, 2 (1.04%) and 15 (7.8%) recurrences were detected in the chemotherapy and in the RPLND arm, respectively, resulting in a 2-year recurrence-free survival rate of 99.46% versus 91.87 % (p = 0.001). The hazard ratio to experience a cancer recurrence with PEB compared to chemotherapy was 7.937. Although RPLND was associated with a significantly higher relapse rate, one has to consider that RPLND was performed in numerous centres with variable surgical experience which might have contributed to the relatively high frequency of intraabdominal relapses as compared to other studies. Quality of surgery, which could not be compared in all of the 61 participating centres (two thirds of patients were recruited by only 12 institutions), is currently recognised as one of the main limitations of RPLND in a national setting. Furthermore, the GTCSG did not collect data on the preservation of antegrade ejaculation in this patient cohort so that no comments with regard to quality of life can be made.

In another large prospective community-based multicenter management program the Swedish and Norwegian Testicular Cancer Project (SWENTOCA) evaluated the therapeutic outcome of 1 cycle adjuvant chemotherapy according to the PEB regime in 745 CSI NSGCT patients (44). Treatment strategy was based on the presence or absence of vascular invasion: if VI was present patients were recommended to undergo 1 course of chemotherapy, if VI was absent patients could choose between active surveillance or chemotherapy. At a median follow-up of 4.7 years a total of 51 relapses were observed. 41.7% and 13.2% of patients with or without vascular invasion experienced relapse whereas only 3.2% and 1.3% of the patients developed recurrences following 1 cycle of chemotherapy. After a follow-up of more than 4 years, the data seem to be mature and 1 cycle of PEB chemotherapy might become the standard of therapy reducing both the total burden of chemotherapy for high risk clinical stage I NSGCT compared to surveillance or adjuvant therapy with 2 cycles of PEB.

**Retroperitoneal Lymph Node Dissection**

According to the EGCCC and the EAU guidelines, patients unwilling to undergo a surveillance strategy or adjuvant chemotherapy, nerve sparing lymphadenectomy (NS-RPLND) may be performed (16, 25, 45).

Primary RPLND is still widely practice in the United States for high risk patients although less so in Canada and Europe. In support of regional therapy the RP is the usual site of relapse in more than 80% of patients with CS I NSGCT (46). RPLND provides accurate staging information regarding RP lymph node status. With proper selection of patients for RPLND, two-thirds have low burden pathologic stage (pS) II disease, and almost 90% will be cured by surgery only [29]. The rationale for primary nerve sparing RPLND for patients with CS I NSGCT is based on the evidence that it represents the primary metastatic site in more than 80% of patients and that it is also the most frequently involved site of chemoresistant mature teratoma which holds the potential of malignant transformation and late relapse if left unresected (47, 48) Virtually all patients who relapse after primary RPLND are chemotherapy naive and eventually cured by usually 3 cycles of cisplatin-based chemotherapy. Only a minority of CS I NSGCT harbour occult systemic metastatic disease and might be better managed by
inductive systemic chemotherapy. RPLND simplifies follow-up and makes it more liberal. Subsequent RP relapse is rare, and abdominal imaging can be restricted to one baseline CT a few months after surgery. With the introduction of nerve-sparing technique along with various modified templates, antegrade ejaculation rates 90–100% have been reported, with significantly reduced morbidity and virtually unknown mortality (49–51). However, opponents of nerve sparing RPLND argue that up to 75% of patients with CS I NSGCT managed by primary RPLND will undergo unnecessary treatment. However, this only holds true if a nonrisk adapted strategy is chosen in every single CS I patient. Recently, patients selection factors on outcome after primary RPLND have been reported and the application of these parameters might allow a risk-adapted indication RPLND (29). The authors analysed a cohort of 453 patients with CS I to IIB NSGCT who underwent RPLND between 1989 and 2002. Of those, 308 (68%) and 122 (27%) presented with CS I and CS IIA disease, respectively. Interestingly the frequency of clinical stage I patients increased significantly over time from 65% to 76% (p = 0.03) in the years 1989 to 1998 and 1999 to 2002, respectively, which might be the result of improved imaging studies. Whereas the frequency of mature teratoma remained fairly constant in the two time periods (22% vs 21%) the number of patients with low volume disease (pN1) increased significantly from 40% to 64% (p = 0.01) so that adjuvant chemotherapy could be spared in more patients. 217 (70%) patients of the 308 CS I NSGCTs demonstrated true pathological stage I disease after RPLND. The 4-year progression-free probability in this cohort was 97%; the risk of systemic progression decreased from 14% before 1999 to 1.3% after 1999 suggesting an improved risk stratification for systemic disease based on the selection criteria developed after critical analysis of the first patient cohort being treated between 1989 and 1999. For CS I NSGCT elevated postorchiectomy tumour markers appear to be associated with a significantly increased risk of progression which was as high as 72%. The question, however, remains if patients with embryonal carcinoma predominance and/or lymphovascular invasion should undergo RPLND or primary chemotherapy due to an anticipated high risk of systemic relapse following locoregional surgical treatment. Stephenson et al. (46) analysed the outcome of 267 patients with CS I and CS IIA NSGCTs with one or two of the aforementioned risk factors who underwent nsRPLND. ECA and VI were present in 31% of the patients and ECA without VI was identified in 10% whereas 58% demonstrated VI without ECA. 129 (66%) patients with CS I and 26 (37%) with CS IIA had pathological stage I disease. 112 patients demonstrated lymph node metastases and 60 (54%) and 52 (46%) demonstrated pN1 and pN2 disease, respectively. The presence of both risk factors was associated with a significantly higher risk of retroperitoneal metastases (54% versus 37%, p = 0.009), however the risk to harbour pN2 disease was not significantly increased. Patients with pathological stage I were followed actively and did not receive adjuvant chemotherapy whereas 22% and 83% of patients with pN1 and pN2 disease received adjuvant cytotoxic treatment with 2 cycles, respectively. All patients remained disease-free during the complete follow-up period. 16% of pathological stage II patients had teratoma in the retroperitoneum which would not have been eliminated by primary chemotherapy. 211 patients did not receive adjuvant chemotherapy and 26 (12.3%) patients experienced relapse with 4 recurrences developing in the retroperitoneum due to a modified template resection. The 5-year progression-free survival probability including a full bilateral template would be 90%. All relapsing patients could be salvage by 4 cycles EP chemotherapy. Summarizing the data of the total cohort of 267 patients, 80 (29.9%) CS I/IIA high risk patients received either adjuvant or salvage chemotherapy. If only high risk CS I NSGCT are considered an estimated 89% would have been free of progression 5 years after chemotherapy.

In a similar approach, Nicolai et al. (52) reviewed their experience of primary RPLND with no adjuvant chemotherapy in a cohort of 322 consecutive CS I NSGCT who were followed for a median time of 17 years. 262 (81.4%) patients were staged as pathological stage I whereas 41 (12.7%) and 19 (5.9%) patients demonstrated pathological stage IIA and IIB, respectively. 50 patients (15.5%) developed a recurrence with 96% occurring the first 2 years of follow-up. The majority of relapses (n = 44) were located outside the retroperitoneum, whereas 6 and 4 relapses developed in the retroperitoneum and in the contralateral tests. 271 (84.1%) patients of the total cohort did not experience relapsing disease including 68.3% of the patients with pathological stage IIA/B. Based on multivariate analysis, presence of vascular invasion, percentage of embryonal carcinoma > 50%, presence of lymph node metastases increased the probability of relapses by the factor 2.7, 3.5 and 2.9, respectively.

Rassweiler et al. (53) assessed the role of laparoscopic RPLND in the management of CS I NSGCT reviewing the literature comprising a total of more than 800 patients. Whereas no significant differences with regard to complications could be observed when compared to open RPLND, it became evident that of more than 90% of patients with positive
lymph nodes underwent adjuvant chemotherapy making laparoscopic RPLND to a mere staging surgery. However, the laparoscopic approach is feasible is highly specialized centres, the curative potential of this approach still has to be evaluated.

Although rare with an incidence of only 2.5%, clinical stage I mature teratoma of the testis harbour a risk of about 16% (54, 55) for retroperitoneal lymph node metastases. The majority of these patients will demonstrate teratomatous elements in the retroperitoneal lymph node metastases, so that nerve sparing RPLND represents the treatment of choice.

When discussing nerve-sparing RPLND as primary treatment option in patients with CS I NSGCT, potential surgery-related complications have to be considered. Quite recently, the German Testicular Cancer Study Group evaluated the outcome of 239 CS I NSGCT who underwent nerve sparing RPLND (56). Minor complications and major complications were observed in 14.2% and in 5.4%, respectively. Antegrade ejaculation could be preserved in 93.3% of the patients and the frequency of ejaculation correlated significantly with the experience of the single surgeon. 14 (.8%) patients developed relapses with the majority (n = 11) being located in the extraperitoneal areas.

In summary, nerve sparing RPLND seems to cure about 85% to 90% of patients with high risk CS I NSGCT. Whereas, 67% of low risk NSGCT are overtreated due to true pathological stage I in 70% of the patients and a low systemic recurrence rate of 3%, high risk patients might benefit from surgery.

**Summary of treatment options for clinical stage I NSGCT**

According to the current guidelines, active surveillance, primary chemotherapy and nerve sparing RPLND represent 3 treatment options with the same high cure rate of about 100% but significantly different long-term complications. As demonstrated, active surveillance can be performed in low risk and in high risk NSGCT with an anticipated relapse rate of about 15% and 50%. The majority of patients will relapse with good and intermediate prognosis tumours which have to be treated with 3 to 4 cycles chemotherapy. About 25% to 30% of these patients will have to undergo postchemotherapy RPLND for residual masses. Primary chemotherapy with 1-2 cycles PEB is a therapeutic option for high risk clinical stage I NSGCT associated with a recurrence rate of only 2-3% and a minimal acute and long-term toxicity rate. Nerve sparing RPLND, if performed properly, will cure about 85% of all high risk patients with clinical stage I NSGCT without the need for chemotherapy.

Although armchair calculations of the odds of cure and toxicity associated with the various treatment options can be performed, recommendations about the most optimal therapy in clinical stage I NSGCT remain controversial. There seems to be a consensus that active surveillance is the treatment strategy of choice for CS I low risk patients. However, there is no clear cut recommendation in high risk patients. Each treatment has its own advantages and disadvantages which have to be discussed thoroughly with the patient. If, however, the positive results of 1 cycle of PEB can be validated, it will become the standard cytotoxic approach for clinical stage I NSGCT.

**REFERENCES AND RECOMMENDED READINGS**

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