Clinical Urology
International Braz J Urol Vol. 34 (6): 715-724, November - December, 2008

Long-term Clinical Outcome in Patients with Stage-I Nonseminomatous Germ Cell Cancer. A Critical Review of Own Treatment Modalities in a Retrospective Study

Sandra Seseke, Silke Bierwirth, Arne Strauss, Rolf-Hermann Ringert, Florian Seseke

Department of Urology (SS, SB, AS, RHR), Georg-August-University, Gottingen, Germany, and Department of Urology (FS), Martha-Maria Hospital, Halle, Germany

ABSTRACT

Purpose: The optimal management of patients with clinical stage I non-seminomatous germ cell testicular cancer (NSGCT I) was considered controversial until the European Germ Cell Cancer Consensus Group determined unambiguous treatment strategies. In order to assess the long-term outcome we evaluated the data of patients with NSGCT I.
Materials and Methods: In a retrospective evaluation, we included 52 patients with a mean age of 26 years (range 15-58) who were treated with different modalities at our department between 1989 and 2003. Mean follow-up was 5.9 years (range 2-14 years). After orchiectomy, 39 patients were treated with chemotherapy, 7 patients underwent retroperitoneal lymph node dissection and 6 men were managed using a surveillance strategy. Survival, recurrence rate and time of recurrence were evaluated. The histological staging and treatment modality was related to the relapse.
Results: Tumor specific overall mortality was 3.8%. The mortality and relapse rate of the surveillance strategy, retroperitoneal lymph node dissection and chemotherapy was 16.7% / 50%, 14.3% / 14.3% and 0% / 2.5% respectively. All relapsed patients in the surveillance group as well as in the RPLND group had at least one risk factor for developing metastatic disease.
Conclusions: Following the European consensus on diagnosis and treatment of germ cell cancer in patients with NSGCT Stage I any treatment decision must be individually related to the patient according to prognostic factors and care capacity of the treating centre. In case of doubt, adjuvant chemotherapy should be the treatment of choice, as it provides the lowest risk of relapse or tumor related death.

Key words: *testis; testicular neoplasms; chemotherapy; surveillance; retroperitoneal lymph node dissection; outcomes assessment*
Int Braz J Urol. 2008; 34: 715-24

INTRODUCTION

The incidence of testicular cancer has increased over the last 50 years and is the most common malignancy in men in the 15-35 year age group. Nonseminomatous germ cell cancer occurs in slightly younger patients than in those with seminomas. Stage 1 disease is treated initially by orchiectomy, which assures accurate histological diagnosis. The importance of this pathological staging is reflected in the decision for the adjuvant treatment modalities. Although standardized recommendations for follow-up are not defined, patients without increased relapse risk such as vascular or lymphatic invasion, predominant component of embryonal carcinoma and undifferentiated elements (1), are recommended for

active surveillance. The relapse rate in this treatment strategy is approximately 30 %. Metastases will occur in the retroperitoneum in 54-78% and in the lung in 13-31% of the relapsed patients (2) and can be salvaged with cisplatin-based chemotherapy protocols (3). Following the recommendations of the European Germ Cell Cancer Consensus Group, in patients with reservations against the surveillance strategy, needing a high rate of compliance, adjuvant chemotherapy is the treatment of choice (relapse rate 3%). In case of reservations against the two afore mentioned options, nerve sparing retroperitoneal lymph node dissection (NS-RPLND) is suggested (3).

Vascular invasion is the most important prognostic indicator for developing metastatic disease in up to 48%. Patients with risk factors should be given two cycles of BEP (standard dose of cisplatin, etoposide, bleomycin) (3). However, cure rates of about 99% can be reached in patients with clinical stage I non-seminomatous germ cell testicular cancer (NSGCT I) with or without risk factors, independently of the treatment strategy.

Any decision for the optimal adjuvant treatment modality for non-seminomatous Stage 1 needs close co-operation between physician and patient to make sure, that the patient's compliance is in line with the chosen therapy. If a patient cannot deal with the psychological distress of a recurrence rate of approximately 30% (low risk) to 58% (high risk) (4) or if the compliance for regular follow- up intervals must be questioned, an adjuvant treatment should be preferred instead of the surveillance strategy.

In this study we retrospectively reviewed the patients with NSGCT I treated at our urological department from 1989 to 2003 to evaluate the long-term outcome. The results were compared with those obtained from other studies in the literature. Preferentially, we offered adjuvant chemotherapy with excellent cure rates, accepting an overtreatment in selected patients. The aim of this study was to critically review the applied treatment strategies with special emphasize on the relapsed patients.

MATERIALS AND METHODS

Patients - Between 1989 and 2003, 55 patients with NSGCT I were treated. Mean age was 26 years (range 15-58). Mean follow-up was 7.4 years (range 2-16 years).

Data acquisition - The records were reviewed for histological classification, clinical and pathological staging, serum tumor markers, adjuvant therapy and last follow-up.

Inclusion criteria - All patients had a histologically proven non-seminomatous germ cell cancer. Forty-three of the evaluated patients had a pT1 tumor, in 8 patients the histological work-up showed a pT2 stage and 1 patient had a pT3 tumor. Staging evaluations (chest X-ray, pre- and postoperative serum tumor markers, abdominal CT scan) excluded metastatic disease.

Therapy and follow-up - All patients had undergone radical orchiectomy. Following orchiectomy 39 patients were treated with chemotherapy of two (n = 29) or three (n = 5) courses of bleomycine, etoposide and cisplatin (BEP), or, in case of prior lung problems ifosfamide instead of bleomycin (n = 5). Seven patients underwent retroperitoneal lymph node dissection and 6 men were managed in a surveillance strategy. Follow-up evaluations included physical examination, chest radiographs, serum tumor markers, abdominal and testicular ultrasound and abdominal CT scan periodically as seen in Table-1. Patients were encouraged to be followed for at least 10 years.

Data evaluation - All patients with a documented follow-up of at least two years were included. Three men were lost to follow-up. The data of 52 patients could be evaluated based on a follow-up until June 2008. Evaluation included survival, recurrence-rate and time of recurrence. The previous histological staging and treatment modality was related to the relapse.

RESULTS

Up to the evaluation date three patients had died. One of these developed gastric cancer and died 9 years after treatment for non-seminomatous germ cell cancer. The initial histological workup showed a pT1 tumor and the patient was treated by retroperitoneal lymph node dissection (RPLND) after radical orchiectomy.

Table 1 *– Follow-up evaluations.*

Year	**1**				**2**				**3**		**4**		**5**		**> 5**
Month	3	6	9	12	15	18	21	24	30	36	42	48	54	60	Once a year
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum tumor markers	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Chest radiographs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Ultrasound abdomen/testis	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
CT scan abdomen		x		x		x		x		x		x		x	

Two of the 52 patients (3.8%) died related to their underlying malignancy (Table-2).

As regards RPLND - Six patients from the RPLND group (n = 7) were disease free and well at the time of evaluation. Five of them had a pT1 and the other a pT2 tumor. The relapsed patient who had a pT1 tumor with teratoma and embryonal carcinoma was initially treated by orchiectomy. Subsequently an adjuvant modified RPLND was performed. Histological work-up did not show any pathologic lymph nodes. Twelve months after the diagnosis a recurrence occurred revealed by serum tumor markers. Initially, the patient refused further imaging and therapy. One year later, he had a CT scan showing a compression of the vena cava with a large retroperitoneal mass. Chemotherapeutic treatment (cisplatin, etoposide, ifosfamid) was started and a secondary RPLND was performed after completing this therapy. The histological workup revealed mature teratoma. Six months later elevated serum tumor markers again indicated tumor recurrence again. Because the CT scan did not show any pathology, biopsies of the remaining testis were performed that histologically showed only atrophic parenchyma without malignancy. However, another 2 months later the abdominal CT scan showed multiple liver metastases. A high dose chemotherapy (POMP-ACE: prednisone, vincristine, methotrexate, mercaptopurine, adriamycin, cyclophosphamide, etoposide) followed but tumor mass could not be downsized. The patient refused any further therapy and died of his disease a few months later.

Surveillance - Six of our patients entered a surveillance protocol. Three of them relapsed. Histological evaluation after orchiectomy had shown a pT 2 tumor with seminomatous and embryonal cell components in one of the relapsed patients. Despite regular follow-up, two years after primary diagnosis, retroperitoneal recurrence of the tumor was detected when the patient complained of flank pain and weight loss. Tumor markers were increased. At first, the patient refused any further imaging and therapy. After one year, the CT scan showed multiple metastases in the retroperitoneum and upper abdomen. Due to renal insuffiency a carboplatin (instead of cisplatin) based chemotherapy was initiated. Nevertheless, a few days later the patient died of complications caused by the chemotherapy with renal failure and tumor lysis syndrome.

Relapse of the tumor was recorded in another two patients (Table-2). The first patient had been managed in a surveillance strategy after orchiectomy for a pT1 tumor with components of embryonal carcinoma (predominant) and seminoma that relapsed at 11 years after initial treatment. Serum tumor markers were prominent in the follow-up. CT scan showed enlarged para-aortic lymph nodes. After chemotherapy treatment with cisplatin, etoposide and bleomycin he is

Table 2 *– Recurrences in the follow-up of 52 patients with NSGCT stage I.*

Pt. No.	Pathologic Stage, Histological Components	Adjuvant Therapy	Time to Recurrence	First Evidence for Relapse	Recurrence Site	Treatment	Results
1	pT1, teratoma, embryonal carcinoma	RPLND	12 month	serum tumor marker	retroperitoneum	chemotherapy, surgery	relapse after 6 month, refused therapy for 12 month, tumor bulk compressing the vena cava, chemotherapy, disease progressed, died
2	pT2, seminoma, embryonal carcinoma	surveillance	24 month		retroperitoneum	chemotherapy	refused therapy for 12 month, metastases retroperitoneum and upper abdomen, died during chemotherapy (tumor lysis with renal failure)
3	pT1, seminoma, embryonal carcinoma	surveillance	11 years	serum tumor marker	para-aortic lymph nodes	chemotherapy	disease free
4	pT2, yolc sac, embryonal carcinoma	surveillance	12 month	CT, serum tumor marker	interaortocaval lymph nodes	chemotherapy, surgery	disease free
5	pT1, embryonal carcinoma	BEP	24 month	serum tumor marker	retroperitoneum?	chemotherapy	disease free

disease-free up to now at a follow-up of 6 years since diagnosis.

The second patient presented with a large bulk of interaortocaval lymph node metastases and elevated serum tumor markers (AFP and ß-HCG) one year after primary diagnosis of a nonseminomatous germ cell tumor with components of yolk sac tumor and predominant embryonal carcinoma. The relapse was treated with three courses of bleomycin, etoposide, and cisplatin (BEP) and residual masses were

removed by secondary RPLND. Histological examination revealed mature teratoma tissue. Seven years postoperatively the patient remained disease free.

Chemotherapy – Thirty-nine patients underwent adjuvant chemotherapy after primary orchiectomy. One of them relapsed.

The contralateral biopsy of the patient performed at the time of orchiectomy of a pT1 tumor showed intratubular germ cell neoplasia (TIN). Radiation treatment of the remaining testis with a total dose of 20 Gy followed. One year later another biopsy of the testis did not show any malignancy. Another year later, serum tumor marker increased. The CT scan did not detect any pathologically enlarged lymph nodes. A further biopsy of the testis followed. The histological workup again showed a TIN. Assuming that it would be a generalized problem rather than a local tumor growth, the patient was treated with two courses of chemotherapy (BEP) and we included him in the recurrence group. He remained disease free at a follow-up of 5 years (Table-2, Pt. 5). Taken together, the incidence of TIN of the contralateral testis in our group of patients was 3% (1 of 33 biopsies, others refused biopsy or orchiectomy was performed in an external hospital without obtaining a biopsy). Our patient's cohort included 20 patients with one or more risk factors (embryonal carcinoma and/or vascular invasion) and 19 without.

COMMENTS

The incidence of testicular cancer has been increasing in recent years (5). The optimal management of these patients was considered controversial until the European Germ Cell Cancer Consensus Group primarily established clearly defined diagnostic and therapeutic strategies in 2004 and then updated in 2008 (3). Recommendations for active surveillance in patients with low recurrence risk (without evidence of vascular invasion, a predominant component of embryonal cell carcinoma or undifferentiated element) are uniformly accepted as long as the patients compliance is in line with the repeated diagnostic testing to detect relapses at an early stage (3,6). However, for patients who cannot manage the psychological distress of recurrence rates between 14% and 22 % (1) or those not candidates for surveillance for other reasons the adjuvant management remains controversial. Chemotherapy or retroperitoneal lymph node dissection (RPLND) are possible options. There is no consensus about, which strategy should be preferred. Krege et al. suggest chemotherapy with two cycles of BEP (3), whereas Stephenson and Sheinfeld prefer RPLND in these patients (6). In cases with a high risk of recurrence the same recommendation dilemma exists. Because of relapse rates up to 50%, most authors suggest an adjuvant treatment (7). However, some authors propose active surveillance even in this patients group (8).

The major advantage of the surveillance strategy is that up to 86% of the patients do not need any further treatment. Furthermore, relapses can be cured in nearly 100% of cases. However, the problem might be the patient's compliance and the psychological distress of the recurrence rates with a more intensive chemotherapy in case of relapse. A strict follow-up scheme and a compliant patient are mandatory otherwise an adjuvant treatment has to be recommended.

Advantages of RPLND over chemotherapy are the surgical removal of chemoresistant teratoma, as its biological potential is unpredictable, and, furthermore, the lower long-term toxicity (6). Relapses can be cured with chemotherapy in nearly all cases. Otherwise, patients will be exposed to surgery-associated side effects. The retrograde ejaculation with consecutive potential infertility based on surgical damage of the postganglionic sympathetic fibers (Th 12-L 3) forming the hypogastric plexus near the aortic bifurcation is an essential problem for young patients. However, even selective RPLND has significantly reduced but not eliminated ejaculatory problems (1).

The major disadvantage of adjuvant chemotherapy is potential overtreatment in up to 70% of unselected Stage I patients. Short-term side effects (Nausea, vomiting) can be managed with potent clinical agents and leucocytopeny and thrombozytopeny are usually mild. Long-term side effects are a possibly decreased fertility and the development of secondary malignancies, as seen in high dose chemotherapy with etoposide (9). Concerning fertility, it has to be considered that in patients with malignant germ cell tumors, semen quality of the unaffected contralateral testes is significantly worse than in the healthy male

(10) even before any chemotherapeutic treatment was applied. Furthermore, whether spermatogenesis is affected irreversibly by chemotherapy is determined by the cumulative dose of cisplatin. Pont and co-workers point out that the dose of even four courses of BEP is unlikely to cause any irreversible damage as the cisplatin dose generally remains below the critical dose of 400 mg/m^2 (11). Secondary malignancies are potentially caused by etoposide. The risk should be low because the critical dose is 1500-2000 mg/m^2 and the applied dose in adjuvant BEP will generally remain below (12). Furthermore, platin based therapy increases the risk of cardiovascular events (13). The above-mentioned studies only included patients with three or more courses and late effects seem to be dose dependant.

Considering these various factors, independently of the therapeutic regimen cure rates up to 99% (3) can be reached in patients with NSGCC. The decision about optimal adjuvant treatment after orchiectomy has to include risk factors as well as the patient's wishes and psychological situation and includes surveillance, adjuvant chemotherapy and RPLND.

To evaluate the outcome depending on the treatment strategies and risk factors of our own patients with NSGCT Stage I we retrospectively evaluated patients treated in our department between 1989 and 2003. Our preferred adjuvant modality was a chemotherapeutical treatment with two courses of BEP or ifosfamide instead of bleomycin in case of prior lung problems, accepting a potentially overtreatment in up to 50% of the cases but with very low recurrence rates (3). The minimal follow-up of the patients was defined as at least 2 years because the majority of relapses will occur within this period (14,15).

With respect to the low patient's number and the inhomogeneous group the cancer related mortality of the included 52 patients was 4% and comparable with the data obtained from the literature (16). All the patients relapsed in the retroperitoneum, independently from the chosen adjuvant modality.

Surveillance Group

Three out of six patients managed with a surveillance strategy after orchiectomy relapsed. Data published in the literature ranged from 30 - 75% (3,14,17) depending on risk factors. Whether adjuvant therapy was not recommended, or the patients primarily decided to active surveillance, or the concerned patients refused any further therapy, remains unclear from the retrospective evaluation of the records. However, all of our relapsed patients had one or two risk factors for developing metastatic disease, questioning the chosen strategy in these patients retrospectively. In two cases embryonal carcinoma was the dominating histological feature in the ablated testes in addition to vascular invasion of the tumor, including the patients retrospectively in the "high risk" group. The other patient did not have any vascular invasion but primarily rather embryonal carcinoma in the resected tumor. Time to recurrence was 1, 2 and 11 years, respectively. There was one tumor related death in these 6 patients on surveillance. At the point of recurrence, the respective patient foremost refused any further diagnosing and therapy (Table-2, Pt. 2), presuming that he did not show appropriate compliance to the primarily chosen surveillance strategy. In previous studies the rate was between 1, 2 and 2.8% (8,17). The high value in our group might be explained by the low number of patients included in this evaluation. After initiating an intensified chemotherapy one year after the metastatic spread the patient died because of chemotherapeutic induced side effects.

From the patients under surveillance which did not relapse one was "high risk" (embryonal carcinoma) and the other two were "low risk" cases (seminoma and embryonal carcinoma and seminoma, yolk sac tumor and embryonal carcinoma respectively, both with seminoma being the predominant component).

RPLND

Even though it is uncommon, one of our patients treated with RPLND after primary orchiectomy relapsed. Unfortunately, the patient refused any further imaging and therapy after suspicion of recurrence and the large retroperitoneal bulk made it difficult to evaluate the site of relapse. Therefore, it was impossible to assess whether it was an infield recurrence with lymphatic tissue left behind during the primary RPLND or an outside the border of the primary RPLND recurrence, as has also been described by other groups (18). The relapse rate after RPLND reported in the literature was between 5.8 - 21% (18,19). As seen from Table-2 (Pt. 1) the affected

patient, although showing a stage pT1, belonged to the high-risk group as the tumor showed embryonal carcinoma as predominating histological component. Although intensified chemotherapeutic treatment was initiated, the patient died of tumor progression.

Chemotherapy

One of the 39 patients (2.5%) treated with adjuvant chemotherapy relapsed. He suffered from a pT1 teratocarcinoma. Therefore, he initially did not have any risk factors for developing metastatic disease. Additionally, the histological workup showed a TIN of the contralateral testis. He was treated with two courses BEP and a radiation therapy was applied to the remaining testis. Two years later tumor marker increased but imaging did not show enlarged lymph nodes. Another therapy with two courses BEP was given. The patient has remained disease free to date. Comparably, formerly published studies showed a mortality of patients with NSGCT I treated with CTX between 0 and 4% (9,20,21). Relapse rates between 0 and 7% were reported (9,20,21). All these studies administered chemotherapeutic treatment only in high risk patients. Our patient cohort included 20 patients with one or more risk factors (embryonal carcinoma and/or vascular invasion) and 19 without. Retrospectively, most of the patients of the low-risk group were overtreated.

Limitations of the study - The indication for the particularly chosen treatment strategy could not be determined from the retrospectively assessed data. The reason for the inhomogeneous groups remains unclear and results in small numbers of patients especially in the surveillance and RPLND group. Small numbers can affect the reliability and confidentiality of results.

Rate is likely to be imprecise and the comparability of percentages is limited. Nevertheless, we attempted to include the data in this context and tied to discuss the results with respect to the low patient's number.

CONCLUSION AND CRITICAL REVIEW

The results of the evaluation of 52 own patients with NSGCT I treated with different adjuvant modalities were comparable with those obtained in the literature. All relapsed patients from the surveillance group had at least one risk factor for developing metastatic disease, presuming them to better candidates for adjuvant chemotherapy. One of these patients seemed to be fairly incompliant and was not a candidate for this follow up scheme retrospectively. Nevertheless, although the treatment strategies for our patients with NSGCT Stage I were highly inconsistent during the chosen observation period of 24 years, neither relapse rates nor mortality were mainly affected.

Considering all the factors involved, the decision for the correct adjuvant approach in patients with stage I nonseminomatous germ cell tumors should include risk factors for developing metastatic disease as well as patient related factors. Furthermore, individual clinical expertise should be considered in the decision. Summarizing the results in line with recent data from the literature, patients with NSGCT I should be treated following the recommendations of the European Germ Cell Cancer Consensus Group (3) avoiding an inhomogeneous therapeutic regimen and providing the optimal treatment for every single patient.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Albers P, Siener R, Kliesch S, Weissbach L, Krege S, Sparwasser C, et al.: Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: results of the German Testicular Cancer Study Group Trial. J Clin Oncol. 2003; 21: 1505-12.
2. Spermon JR, Roeleveld TA, van der Poel HG, Hulsbergen-van de Kaa CA, Ten Bokkel Huinink WW, van de Vijver M, et al.: Comparison of surveillance and retroperitoneal lymph node dissection in Stage I nonseminomatous germ cell tumors. Urology. 2002;59: 923-9.
3. Krege S, Beyer J, Souchon R, Albers P, Albrecht W, Algaba F, et al.: European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer

Consensus group (EGCCCG): part I. Eur Urol. 2008; 53: 478-96.
4. Fosså SD, Moynihan C, Serbouti S: Patients' and doctors' perception of long-term morbidity in patients with testicular cancer clinical stage I. A descriptive pilot study.Support Care Cancer. 1996; 4: 118-28.
5. Bray F, Richiardi L, Ekbom A, Forman D, Pukkala E, Cuninkova M, et al.: Do testicular seminoma and nonseminoma share the same etiology? Evidence from an age-period-cohort analysis of incidence trends in eight European countries. Cancer Epidemiol Biomarkers Prev. 2006; 15: 652-8.
6. Stephenson AJ, Sheinfeld J: Management of patients with low-stage nonseminomatous germ cell testicular cancer. Curr Treat Options Oncol. 2005; 6: 367-77.
7. Böhlen D, Borner M, Sonntag RW, Fey MF, Studer UE: Long-term results following adjuvant chemotherapy in patients with clinical stage I testicular nonseminomatous malignant germ cell tumors with high risk factors. J Urol. 1999; 161: 1148-52.
8. Colls BM, Harvey VJ, Skelton L, Frampton CM, Thompson PI, Bennett M, et al.: Late results of surveillance of clinical stage I nonseminoma germ cell testicular tumours: 17 years' experience in a national study in New Zealand. BJU Int. 1999; 83: 76-82.
9. Chevreau C, Mazerolles C, Soulié M, Gaspard MH, Mourey L, Bujan L, et al.: Long-term efficacy of two cycles of BEP regimen in high-risk stage I nonseminomatous testicular germ cell tumors with embryonal carcinoma and/or vascular invasion. Eur Urol. 2004; 46: 209-14; discussion 214-5.
10. Dieckmann KP, Linke J, Pichlmeier U, Kulejewski M, Loy V; German Testicular Cancer Study Group. Spermatogenesis in the contralateral testis of patients with testicular germ cell cancer: histological evaluation of testicular biopsies and a comparison with healthy males. BJU Int. 2007; 99: 1079-85.
11. Pont J, Albrecht W: Fertility after chemotherapy for testicular germ cell cancer. Fertil Steril. 1997; 68: 1-5.
12. Bokemeyer C, Schmoll HJ: Treatment of testicular cancer and the development of secondary malignancies. J Clin Oncol. 1995; 13: 283-92.
13. van den Belt-Dusebout AW, Nuver J, de Wit R, Gietema JA, ten Bokkel Huinink WW, Rodrigus PT, et al.: Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol. 2006; 24: 467-75.
14. Divrik RT, Akdogan B, Ozen H, Zorlu F: Outcomes of surveillance protocol of clinical stage I nonseminomatous germ cell tumors-is shift to risk adapted policy justified? J Urol. 2006; 176: 1424-29; discussion 1429-30.
15. Klepp O, Dahl O, Flodgren P, Stierner U, Olsson AM, Oldbring J, et al.: Risk-adapted treatment of clinical stage 1 non-seminoma testis cancer. Eur J Cancer. 1997; 33: 1038-44.
16. van der Poel HG, Sedelaar JP, Debruyne FM, Witjes JA: Recurrence of germ cell tumor after orchiectomy. Urology. 2000; 56: 467-73.
17. Hendry WF, Norman A, Nicholls J, Dearnaley DP, Peckham MJ, Horwich A: Abdominal relapse in stage 1 nonseminomatous germ cell tumours of the testis managed by surveillance or with adjuvant chemotherapy. BJU Int. 2000; 86: 89-93.
18. Heidenreich A, Albers P, Hartmann M, Kliesch S, Kohrmann KU, Krege S, et al.: Complications of primary nerve sparing retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: experience of the German Testicular Cancer Study Group. J Urol. 2003; 169: 1710-4.
19. Stephenson AJ, Bosl GJ, Bajorin DF, Stasi J, Motzer RJ, Sheinfeld J: Retroperitoneal lymph node dissection in patients with low stage testicular cancer with embryonal carcinoma predominance and/or lymphovascular invasion. J Urol. 2005; 174: 557-60; discussion 560.
20. Oliver RT, Ong J, Shamash J, Ravi R, Nagund V, Harper P, et al.: Long-term follow-up of Anglian Germ Cell Cancer Group surveillance versus patients with Stage 1 nonseminoma treated with adjuvant chemotherapy. Urology. 2004; 63: 556-61.
21. Pont J, Albrecht W, Postner G, Sellner F, Angel K, Höltl W: Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. J Clin Oncol. 1996; 14: 441-8.

Accepted after revision:
August 14, 2008

Correspondence address:
Dr. Sandra Seseke
Department of Urology
Georg-August-University
Robert-Koch-Strasse 40
37075 Göttingen, Germany
Fax: + 0049 551-396165
E-mail: srebman@gwdg.de

EDITORIAL COMMENT

Overall, the paper lacks strength due to the small number of patients in the RPLND and surveillance arms. In the introduction it is stated that "in patients with reservations to surveillance, adjuvant chemotherapy is the treatment of choice". In my opinion this is not true. Furthermore, in the discussion it states that "chemotherapy or RPLND are possible options". Overall there is not survival difference between any of the 3 modalities and RPLND is curable in high risk patients.

Dr. S. D. Beck
Department of Urology and Oncology
Indiana University Medical Center
Indianapolis, Indiana, USA
E-mail: sdwbeck@iupui.edu

EDITORIAL COMMENT

The introduction of cisplatin-based combination chemotherapy has revolutionized the treatment of metastatic testicular cancer. Owing to the high success rate in the salvage of disseminated cancer, it has become reasonable to argue for managing clinical Stage I nonseminomatous germ cell testicular tumors (CS I NSGCTT) patients with orchiectomy alone followed by surveillance. Patients, who relapse are treated with systemic chemotherapy, whereas those, who do not relapse, are spared unnecessary treatment.

The surveillance after orchiectomy alone has gained a lot of popularity in the management of CS I NSGCTT. Preliminary results were enthusiastic, but critical voices have been raised against general use of this option as a routine management. With longer observation, the relapse rate has been found to increase to 25 % or more after orchiectomy. Recent investigations have focused on determining the factors that identify a group of patients at high risk of the relapse, who might therefore benefit from a program other than surveillance.

The optimal management of CS I NSGCTT patients after an orchiectomy has been controversial for several decades, because of the difficulty of distinguishing true Stage I patients from those with occult retroperitoneal and distant metastases. Over the last 20 years, a surveillance strategy has been in practice at various centers to save patients in Stage I from unnecessary treatment-related morbidity. A number of primary tumor prognostic factors have been discovered that may be useful in stratifying CS I patients as to their likelihood of harboring occult disease. Up to 30 % of CS I NSGCTT patients have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy.

The utility of vascular invasion (venous and lymphatic invasion) as a prognostic marker in CS I NSGCTT was first recognized in the 1980`s and during the years it became the main predictor of relapse in CS I NSGCTT managed by surveillance. Importance of embryonal carcinoma as a prognostic factor in low stage NSGCTT was discovered when surveillance studies were analyzed for relapse factors. Therefore, embryonal carcinoma is extremely important as a prognostic marker for occult disease in CS I NSGCTT. The presence of teratoma elements in testicular germ cell tumors has been known to have a favorable impact on prognosis. In contemporary era of prognostic factors in CS I NSGCTT, the presence of teratoma lessens the likelihood of occult disease. Teratomatous elements in the orchiectomy specimen predict for retroperitoneal teratoma, therefore primary RPLND in CS I NSGCTT patients was recommended for cases with the finding of teratoma in the primary

tumor. Patients can be stratified according to risk factors into different prognostic groups with different recurrence rates. According to EAU guidelines on testicular cancer and to reports of the European Germ Cell Cancer Consensus Group risk-adapted treatment is recommended as treatment of first choice in CS I NSGCTT patients, however, there is no worldwide consensus on the management of high-risk CS I NSGCTT. High risk patients, with vascular invasion are recommended to undergo adjuvant chemotherapy with two cycles of BEP regimen, intermediate risk patients are recommended to undergo primary RPLND and low risk patients, without vascular invasion are recommended to undergo surveillance.

It is generally accepted that surveillance is appropriate for patients with a low risk of relapse (without vascular invasion), however, there is no universally accepted standard protocol for surveillance of patients with CS I NSGCTT. The main advantage of surveillance being that 70-86 % of patients do not need any further treatment after orchiectomy. The disadvantages are the psychological and practical difficulties of intense follow-up for some patients.

The interesting article by Seseke et al. describes long-term experiences with CS I NSGCTT. Their information that vascular invasion is the most important prognostic indicator for a risk of developing metastatic disease is correct, but percentage up to 48% is too high. Also the results of the authors that patients managed with a surveillance strategy after orchiectomy showed a relapse rate 50 % is too high. Therefore, the results of authors are not comparable with those obtained in literature because of small number error causes (inhomogeneous number of patients treated by particular therapeutic modalities).

REFERENCES

1. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Horwich A, et al.: EAU Guidelines on Testicular Cancer. EAU, Arnhem 2008. access in: http://www.uroweb.org/fileadmin/tx_eauguidelines/09%20Testicular%20Cancer.pdf
2. Krege S, Beyer J, Souchon R, Albers P, Albrecht W, Algaba F, et al.: European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part I.Eur Urol. 2008; 53: 478-96.
3. Ondrus D, Ondrusova M, Hornak M, Matoska J: Nonseminomatous germ cell testicular tumors clinical stage I: differentiated therapeutic approach in comparison with therapeutic approach using surveillance strategy only. Neoplasma. 2007; 54: 437-42.

Dr. Dalibor Ondrus
Department of Oncology
Comenius University Medical School
St. Elisabeth Cancer Institute
Bratislava, Slovak Republic
E-mail dondrus@ousa.sk