Nonseminomatous germ cell testicular tumors – clinical stage I: differentiated therapeutic approach in comparison with therapeutic approach using surveillance strategy only

D. ONDRUS[1*], M. ONDRUSOVA[2,3], M. HORNAK[4], J. MATOSKA[5]

[1]1st Department of Oncology, Comenius University Medical School, St. Elisabeth Cancer Institute, Heydukova 10, 812 50 Bratislava, Slovak Republic, e-mail: dondrus@ousa.sk; [2]National Cancer Registry of the Slovak Republic, National Health Information Centre; [3]Department of Cancer Epidemiology, Cancer Research Institute, Slovak Academy of Sciences; [4]Department of Urology, Comenius University Medical School; [5]Department of Pathology, St. Elisabeth Cancer Institute; Bratislava, Slovak Republic

Received February 1, 2007

Surveillance after orchiectomy alone becomes popular for the management of clinical stage I nonseminomatous germ cell testicular tumors (CS I NSGCTT). Effort to identify patients at high risk of relapse leads to searching for risk factors of CS I NSGCTT. The aim of the study was to analyse own long-term experiences with different therapeutic approaches in CS I NSGCTT patients according to risk factors of the disease progression and to correlate these results with the group of patients who were treated with surveillance strategy only. From 11/1984 to 12/1991 a total of 145 patients with CS I NSGCTT were treated with surveillance strategy only (group A) and were followed-up to 1/2007. Patients, who had the disease progression, were treated with systemic chemotherapy. The disease progression was experienced in 52 patients (35.9 %). The overall survival rate of the patients in this group was 130/145 (89.7 %). From 1/1992 to 1/2007 a total of 323 patients with CS I NSGCTT were stratified to different risk-adapted therapeutic approaches (groups B1-3) according to histopathologic findings of primary tumor removed by inguinal orchiectomy. 111 patients (group B1) with vascular invasion and majority of embryonal carcinoma component in the primary tumor were treated with adjuvant chemotherapy (2 cycles of BEP). Disease progression developed in two patients (1.9 %). Other patients live without evidence of disease (NED). None of them died. Among 11 patients (group B2) with vascular invasion and majority with teratomatous elements in the primary tumor underwent primary retroperitoneal lymph node dissection (RPLND), 9 were found to be pathological stage I. The disease progression was observed in two patients (18.2 %), they died 87-122 months following orchiectomy. Two patients (18.2 %) with pathological stage II received adjuvant chemotherapy. Other 7 patients live with NED following RPLND. 201 patients (group B3) without vascular invasion have been followed after orchiectomy alone. They were kept under close surveillance, consisting of regular follow-up with tumor markers, chest x-ray and CT of the retroperitoneum. The disease progression was observed in 39 patients (19.4 %), who were treated with BEP chemotherapy. Three of them (7.7 %) died after a mean follow-up of 32.7 months following orchiectomy. The overall survival rate of all patients in group B1-3 was 98.4 %. Introduction of different therapeutic approaches in CS I NSGCTT patients according to risk factors of the disease progression might reduce the overall relapse rate of these patients from 35.9 % (group A) to 19.4 % (group B3) ($P < 0.001$). Surveillance procedure is recommended only in patients without vascular invasion in the primary tumor.

Key words: testicular cancer, surveillance, adjuvant chemotherapy, lymph node dissection

The introduction of cisplatin-based combination chemotherapy has revolutionized the treatment of metastatic testicular cancer [1]. Owing to the high success rate in the salvage of disseminated cancer, it has become reasonable to propose for managing clinical stage I nonseminomatous germ cell testicular tumors (CS I NSGCTT) patients with orchiectomy alone followed by surveillance only [2]. Patients who relapse are treated with systemic chemotherapy, whereas those ones 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 [2, 3, 4], but critical voices have

* Corresponding author

been raised against general use of this option as a routine management [5]. With longer observation, the relapse rate has been found to increase up to 25 % or more after orchiectomy [6, 7]. Recent investigation has 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 [8, 9].

The results of our previous reports [6, 10, 11, 12] indicate, that prognostic factors useful for stratification of CS I NSGCTT patients to different therapeutic approaches may be established. Our recent experience confirmed the presence of vascular invasion in the primary tumor as the most important prognostic factor of the disease progression.

Also patients with the majority of embryonal carcinoma (embryoCa) components had significantly higher probability of relapse than patients with the majority of teratomatous elements in the primary tumor.

According to these prognostic factors we stratified CS I NSGCTT patients for following risk-adapted treatment procedures: 1) patients with vascular invasion and the presence of the majority of embryoCa components may be treated with 2 cycles of adjuvant chemotherapy (BEP regimen), 2) retroperitoneal lymph node dissection (RPLND) should be performed in patients with the presence of vascular invasion and the majority of teratomatous elements in the primary tumor and 3) patients without vascular invasion may be kept under surveillance only.

The aim of present study was to analyze own long-term experiences with different therapeutic approaches in CS I NSGCTT patients according to risk factors of the disease progression and to correlate these results with the group of patients who were treated with surveillance strategy only.

Material and Methods

Group A: The prospective study carried out from 11/1984 to 12/1991, included CS I NSGCTT 145 patients, who were followed-up to 1/2007. None of them had a history of undescended testicle. In all cases orchiectomy was performed by the inguinal approach. The patients were assigned to their respective clinical stage on the basis of physical examination, chest x-ray, CT of the retroperitoneum, postorchiectomy serum levels of AFP and β hCG tumor markers. The criteria for the inclusion into CS I were normal values of these examinations. Informed consent was obtained from all patients. Patients with choriocarcinoma component were not included in the study. The policy of surveillance consisted of a regular follow-up the levels of tumor markers measured monthly, chest x-ray and CT of the retroperitoneum performed at 3-month intervals in the first year. The intervals were prolonged in the following years. Patients who had progression of the disease were treated with systemic chemotherapy (PVB or BEP).

Group B: The prospective study carried out from 1/1992 to 1//2007 included CSI NSGCTT 323 patients, who were followed-up to 1/2007 and stratified to different risk-adapted therapeutic approaches (groups B1-3) according to histopathologic findings of primary tumor removed by inguinal orchiectomy. Group B1: 111 patients with vascular invasion and prevailing of embryonal carcinoma component in the primary tumor were treated with 2 cycles of adjuvant chemotherapy (BEP). BEP regimen consisted of cisplatin 20 mg/m^2/d d1-5, etoposide 120 mg/m^2/d d1-3 and bleomycin 30 mg IV infusion d1, d9, d16. The 2nd cycle was scheduled to begin on the day 21 [13]. Group B2: 11 patients with vascular invasion and majority of teratomatous elements in the primary tumor were treated with primary retroperitoneal lymph node dissection (RPLND). Group B3: 201 patients without vascular invasion were kept under close surveillance only. The policy of surveillance was managed as in group A. The patients who had the disease progression were treated with systemic chemotherapy (BEP).

Statistical analysis was performed by chi-square test and by Kaplan-Meier curve for group A and B3.

Results

Group A: The disease progression was found out in 52 patients (35.9 %) with a mean follow-up of 10.5 months (median, 6.5 months, range, 3-100) (95 % CI 6.43-14.57). Fifteen patients (28.8 %) of them died with a mean follow-up of 90.5 months (median, 94 months, range, 8-214) after orchiectomy all. Other patients were followed-up without evidence of disease (NED) by mean of 232 months (range, 182-267). The overall survival rate of all patients in group A was 130/145 (89.7 %).

Group B1: The disease progression was found out in two patients (1.8 %) with a mean follow-up of 31 months (range, 19-43) all. Other patients were followed-up with NED by mean of 72.4 months (range, 2-175).

Group B2: Two patients (18.2 %) with pathological stage II received adjuvant chemotherapy. Other two patients with pathological stage I had the disease progression (18.2 %) with a mean follow-up of 9 months, they died 84-110 months after orchiectomy all. Other patients were followed-up after RPLND with NED by mean of 147.6 months (median, 158 months, range, 96-177).

Group B3: The disease progression was found out in 39 patients (19.4 %) with a mean follow-up of 11.8 months (median, 8.5 months, range, 3-72) (95 % CI 7.87-15.7). Three of them (7.7 %) died after a mean follow-up of 32.7 months (range, 12-103). Other patients were followed with NED by mean of 84.9 months (median, 80 months, range, 3-180).

The overall survival rate of all patients in group B1-3 was 98.4 %. Introduction of different therapeutic approaches in CS I NSGCTT patients according to risk factors of the disease progression might reduce the overall relapse rate of CSI NSGCTT patients from 35.9 % (group A) to 19.4 % (group B3) ($P< 0.001$). Thus, we can conclude that the observed risk ratio of the disease progression of group A was statistically

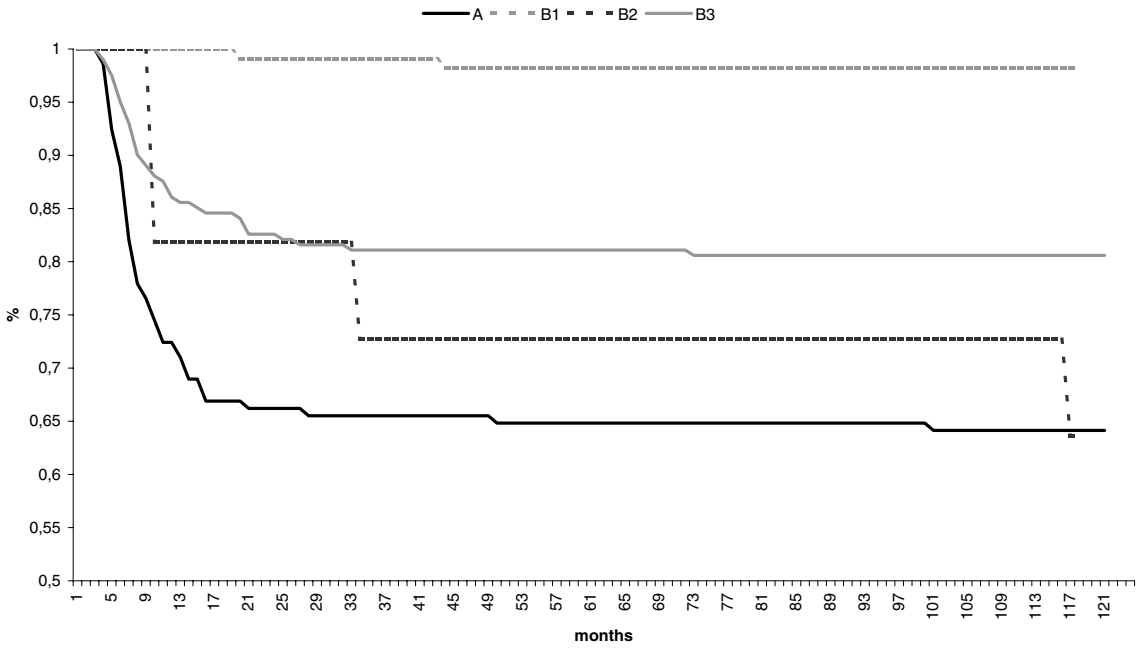

Figure 1. Progression probability in patients with nonseminomatous germ cell testicular tumors – clinical stage I (Kaplan-Meier curve)

significantly higher than the risk of the disease progression in group B3 (fig 1).

Discussion

The optimal management of CS I NSGCTT patients after orchiectomy has been controversial for several decades because of the difficulty of distinguishing actual CS I of the disease in patients from those with occult retroperitoneal and distant metastases. Over the last 20 years, a surveillance strategy was practiced at various centres, just to save patients in CS I from unnecessary treatment-related morbidity [4, 7, 14, 15]. 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 [16]. Up to 30 % of CS I NSGCTT patients have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy.

The association with the presence of occult metastasis was studied for the following histologic and clinical characteristics: vascular invasion of tumor cells, histology of the primary tumor, T-stage and the size of the primary tumor, preorchiectomy levels of AFP and âhCG, and the patients' age.

The utility of vascular invasion (venous and lymphatic invasion) as a prognostic marker in CS I NSGCTT was first recognized in the 1980s [17] and during the years it has became the main predictor of relapse in CS I NSGCTT managed by surveillance only [18].

The importance of embryoCa as a prognostic factor in low stage NSGCTT was discovered when surveillance studies were analyzed for relapse factors. Peckham et al. [2] established the importance of embryoCa in their initial surveillance report. Wishnow et al. [9] were the first, who did a quantitative analysis of percentage of embryoCa extent.

Allhoff et al. [19] studied CS I NSGCTT patients using semiquantitative percentage of embryoCa of two categories (less than 50 % and 50 % or more); they found 50 % or more of embryoCa to be significant for the relapse on surveillance by univariate analysis.

So, the embryoCa is extremely important as a prognostic marker for occult disease in CS I NSGCTT. An experienced reference pathologist should do a careful assessment for embryoCa (as well as vascular invasion), including the percentage of embryoCa [16].

The presence of teratomatous 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 [20]. When there was 50 % or less of teratoma elements in the primary tumor, the chance of occult nodes at RPLND was 44 %, whereas when there was more than 50 %, the occult node rate was only 11 % [21]. In this study, the percentage of teratomatous elements did remain significant on multivariate analysis. Klepp et al. [8] found out that teratoma of any type (mature and immature) was a significant multivariate predictor of occult nodes at RPLND, relapse after a negative RPLND, and overall occult disease in CS I NSGCTT. The risk of positive nodes at RPLND was 20 % in the presence of teratoma and 40 % in its absence. Similarly, patients with teratoma had an 11 % recurrence rate after a negative RPLND, whereas those without this element had

a 24 % recurrence rate. Overall, only 45.4 % of patients without teratomatous elements had true pathological stage I disease versus 71.2 % of those with teratoma.

Other various histologic factors have been suggested as predictors of relapse or occult disease in CS I NSGCTT. The importance of tumor size and T stage has not been confirmed in most multivariate studies of CS I NSGCTT. Only Fung et al. [21] found advanced T stage (T2-T4) to predict occult nodal disease on multivariate analysis.

The association of tumor proliferative activity with occult metastasis in NSGCTT has been determined with several techniques like cytophotometry, flow cytometric analysis and immunohistochemistry. A high percentage of tumor cells stained for proliferating cell nuclear antigen (PCNA) or MIB-1 was associated with a high risk of occult metastasis [22, 23, 24].

Therefore, the patients can be stratified according to risk factors into different prognostic groups with different recurrence rates. According to EAU Guidelines on testicular cancer the risk-adapted treatment is recommended as a treatment of the first choice in CS I NSGCTT patients [25], however, there is no worldwide consensus on the management of high-risk CS I NSGCTT [26]. 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 only.

Primary chemotherapy following orchiectomy for high-risk CS I NSGCTT with the first significant data was published by Cullen et al. [27]. Several studies involving 2 cycles of BEP chemotherapy have been reported [27, 28, 29] showing a relapse rate of 2.7–4.0 %. Our experience shows only 1.9 % relapse rate following adjuvant chemotherapy. Chemotherapy following orchiectomy for CS I NSGCTT results in the lowest relapse rates [30]. In an effort to limit potential over-treatment and treatment related toxicity, Schefer et al. [31] presented their results of a single cycle of BEP adjuvant chemotherapy. After a median follow-up of 32 months (range 4-63) with at least 70 % of patients having two years of follow-up, only one relapse (2.3 %) was seen at 11 months after adjuvant therapy. The isolated relapse occurred in the mediastinum and lungs. The results after one cycle of chemotherapy are not worse than after 2 cycles [32]. The results need to be replicated in a larger cohort of patients to define the relapse rate more accurately. This approach is soon to be tested in a large multicentre trial co-ordinated by the German Testicular Cancer Study Group randomizing patients between one and 2cycles [31].

Primary retroperitoneal lymph node dissection was considered to be the gold standard in CS I NSGCTT [33]; it has remained a viable up-front option after orchiectomy. RPLND provides both accurate staging and curable treatment for microscopic stage II disease [34]. Among CS I NSGCTT patients undergoing RPLND, 70-77 % is found to be pathological stage I, while lymph node metastases are found in the remainder. Most males with pathological stage II disease end up receiving adjuvant chemotherapy [35]. Our experience shows pathological stage II in 18.2 % of patients in group B2. Primary RPLND results in about 10 % absolute reduction and 33 % relative reduction in the risk of needing chemotherapy compared to surveillance only in the average patient [30]. Teratomatous elements in the orchiectomy specimen predict for retroperitoneal teratoma. Foster et al. [36] recommend primary RPLND in CS I NSGCTT patients with the finding of teratoma in the primary tumor. Some studies declare that primary RPLND provides several advantages over induction chemotherapy for these patients [35]. First, RPLND provides accurate pathologic staging and thus more clearly defines subsequent treatment requirements. Second, relapses in the retroperitoneum are rare (less than 2 %) after a properly performed RPLND [33, 37]. Stephenson et Sheinfeld [35] performed primary RPLND for CS I NSGCTT and over 90 % of relapses occurred within the first 12 months, 84 % of relapses occurred in the lungs or were associated with serum tumor marker elevation, and all relapsing patients were alive and continuously with NED after the treatment for relapse. So, postoperative follow-up of these patients simplified as routine retroperitoneal CT imaging is unnecessary. Third, the eradication of all disease in the retroperitoneum significantly reduces the risk of late relapse events. The incidence of late relapse after primary RPLND for CS I was 0.6 % (38), all late relapses occurred in the lungs, and each patient was cured after thoracotomy and resection. Fourth, retroperitoneal teratoma is present in 20-30 % of patients with pathologic stage II and it is resistant to chemotherapy. Although mature and immature teratomas are histologically benign, the biological potential is unpredictable and thus, there is benefit to complete surgical resection by primary RPLND. Fifth, primary RPLND is associated with negligible mortality and minimal morbidity rates when performed by experienced surgeons [39]. The most consistent long-term morbidity of RPLND is the loss of ejaculation, and consequently, potential fertility. To reduce the morbidity of RPLND, several investigators evaluated the role of minimally invasive techniques in testicular cancer (laparoscopic RPLND) [40]. Spermon et al. [41] detected the disease progression in 70 % of patients in the first year, 78 % of relapses were located retroperitoneally when the surveillance strategy was used. Our study confirmed these results; the disease progression was detected in 76.3 % of patients in the first year.

It is generally accepted that surveillance is appropriate for the 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 [42]. The main advantage of surveillance is that 70-86 % of patients do not need any further treatment after orchiectomy [26, 43, 44]. The disadvantages are the psychological and practical difficulties of intense follow-up for some patients. Our experience shows, that the disease progression was observed in only 19.4 % of patients.

Most NSGCTT patients have impaired spermatogenesis prior to treatment, with the degree of impairment being proportional to the stage of disease. In our preliminary report [10], low sperm counts before orchiectomy have been identified as a factor showing a significant correlation with the disease progression. It has not been confirmed however by other studies dealing with surveillance policy in CS I NSGCTT. In non-relapsing testicular cancer cases on surveillance only, initially reduced spermatogenesis recovers after the first year after orchiectomy [45].

There is a paucity of studies directly assessing ejaculatory function following the chemotherapy. Jonker-Pool et al. [46] demonstrated that 21.5 % of patients on adjuvant chemotherapy had some degree of ejaculatory dysfunction compared to a similar group of patients undergoing surveillance only; however Bőhlen et al. [47] concluded their study that 2 cycles of cisplatin based adjuvant chemotherapy do not seem to affect adversely fertility or sexual activity. Ejaculatory function can be preferentially preserved with primary RPLND if one performs a quality nerve sparing dissection. However, if the patient is at low risk for node positive disease and the technical skills of the surgeon do not allow performance of this type of RPLND, a surveillance protocol should be recommended to maximize ejaculatory function preservation [48].

Conclusions

According to our recent experience we confirm, that surveillance only policy is recommended only in CS I NSGCTT patients without vascular invasion in the primary tumor.

References

[1] EINHORN LH, DONOHUE JP. Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 1977; 87: 293–298.

[2] PECKHAM MJ, BARRETT A, HUSBAND JE. et al. Orchidectomy alone in testicular stage I nonseminomatous germ cell tumors. Lancet 1982; 2: 678–680.

[3] JOHNSON DE, LO RK, von ESCHENBACH AC et al. Surveillance alone for patients with clinical stage I nonseminomatous germ cell tumors of the testis: preliminary report. J Urol 1984; 131: 491–493.

[4] SOGANI P, WHITMORE WF, HERR HW et al. Orchiectomy alone in the treatment of clinical stage I nonseminomatous germ cell tumor of the testis. J Clin Oncol 1984; 2: 267–270.

[5] THOMPSON PI, NIXON J, HARVEY VJ. Disease relapse in patients with stage I nonseminomatous germ cell tumor of the testis on active surveillance. J Clin Oncol 1988; 6: 1597–1603.

[6] ONDRUS D, HORNAK M. Orchiectomy alone for clinical stage nonseminomatous germ cell tumors of the testis (NSGCTT): a minimum follow-up period of 5 years. Tumori 1994; 80: 362–364.

[7] STURGEON JFG, JEWETT MAS, ALISON RE et al. Surveillance after orchiectomy for patients with clinical stage I nonseminomatous testis tumors. J Clin Oncol 1992; 10: 564–568.

[8] KLEPP O, OLSSON AM, HENRIKSON H et al. Prognostic factors in clinical stage I nonseminomatous germ cell tumors of the testis: multivariate analysis of a prospective multicenter study. J Clin Oncol 1990; 8: 509–518.

[9] WISHNOW KI, JOHNSON DE, SWANSON, DA et al. Identifying patients with low risk clinical stage nonseminomatous testicular tumors who should be treated by surveillance. Urology 1989; 34: 339–343.

[10] ONDRUS D, HORNAK M, VRABEC J. Low sperm counts as a prognostic factor of progression in stage I non-seminomatous germ cell testicular tumours. Br J Urol 1988; 62: 82–84.

[11] ONDRUS D, GONÇALVES F, KAUSITZ J et al. The value of prognostic factors in the management of stage I nonseminomatous germ cell testicular tumors (NSGCTT). Neoplasma 1996; 43: 195–197.

[12] ONDRUS D, MATOSKA J, BELAN V. et al. Prognostic factors in clinical stage I nonseminomatous germ cell testicular tumors: rationale for different risk-adapted treatment. Eur Urol 1998; 33: 562–566.

[13] PECKHAM MJ, BARRETT A, LIEW KH et al. The treatment of metastatic germ cell testicular tumours with bleomycin, etoposide and cisplatin (BEP). Br J Cancer 1983; 47: 613–619.

[14] FREEDMAN LS, JONES WG, PECKHAM MJ et al. Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchiectomy alone. Lancet 1987; 2: 294–8.

[15] HOSKIN P, DILLY S, EASTON D et al. Prognostic factors in stage I nonseminomatous germ cell testicular tumors managed by orchiectomy and surveillance: Implications for adjuvant chemotherapy. J Clin Oncol 1986; 4: 1031–036.

[16] MOUL JW, HEIDENREICH A. Prognostic factor in low-stage nonseminomatous testicular cancer. Oncology 1996; 10: 1359–1374.

[17] PECKHAM MJ, BARRETT A, HORWICH A et al. Orchiectomy alone for stage I testicular nonseminoma. Br J Urol 1983; 55: 754–759.

[18] ALBERS P, SIENER R, KLIESCH S et al. Risk factors for relapse in clinical stage nonseminomatous testicular germ cell tumors: Results of the German Testicular Cancer Study Group trial. J Clin Oncol 2003; 21: 1505–1512.

[19] ALLHOFF EP, LIEDKE S, de RIESE W et al. Assessment of individual prognosis for patients with NSGCT/CSI (abstract). J Urol. 1991; 145: 367A.

[20] SESTERHENN IA, WEISS RB, MOSTOFI FK et al. Prognosis and other clinical correlates of pathologic review in stage I and II testicular carcinoma: a report from the Testicular Cancer Intergroup Study. J Clin Oncol 1992; 10: 69–78.

[21] FUNG CY, KALISH LA, BRODSKY GL et al. Stage I nonseminomatous germ cell testicular tumor: prediction of metastatic potential by primary chemotherapy. J Clin Oncol 1988; 6: 1467–73.

[22] de RIESE WTW, de RIESE C, ULBRIGHT TM et al. Flow-cytometric and quantitative histologic parameters as prognostic indicators for occult retroperitoneal disease in clin-

ical stage I non-seminomatous testicular germ-cell tumours. Int J Cancer 1994; 57: 628–633.

[23] ALBERS P, BIERHOFF E, NEU D et al. MIB-1 immunohistochemistry in clinical stage I nonseminomatous testicular germ cell tumours predicts patients at low risk for metastasis. Cancer 1997; 79: 1710–1716.

[24] LEIBOVITCH I, FOSTER RS, KOPECKY KK et al. Identification of clinical stage A nonseminomatous testis cancer patients at extremely low risk for metastatic disease: a combined approach usining quantitative immunohistochemical, histopathologic, and radiologic assessment. J Clin Oncol 1998; 16: 261–268.

[25] ALBERS P, ALBRECHT W, ALGABA F et al. EAU Guidelines on testicular cancer, Arnhem, EAU Healthcare office 2005.

[26] COFFEY J, BIRTLE AJ, COGILL G et al. A discussion of the biology of testicular cancer and current concepts in the management of stage I and bilateral disease. Clin Oncol (R Coll Radiol) 2005; 17: 441–447.

[27] CULLEN MH, STENNING SP, PARKINSON MC et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumours of the testis: a Medical Research Council report. J Clin Oncol 1996; 14: 1106–1113.

[28] BÖHLEN D, BORNER M, SONNTAG RW et al. 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: 1148–1152.

[29] OLIVER RTD, ONG J, SHAMASH J 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: 556–561.

[30] GILLIGAN T. Changing management of clinical low-stage testicular cancer. Scientific World J 2005; 16: 852–867.

[31] SCHEFER H, MATTMANN S, BORNER M et al. Single course adjuvant bleomycin, etoposide and cisplatin (BEP) for high risk stage I non-seminomatous germ cell tumors (NSGCT) ASCO 36th Annual Meeting, May 20-23, 2000, New Orleans. Procc ASCO 2000: 340 A.

[32] GILBERT DC, NORMAN AR, NICHOLL J et al. Treating stage I nonseminomatous germ cell tumours with a single cycle of chemotherapy. BJU Int 2006; 98: 67–69.

[33] DONOHUE JP, THORNHILL JA, FOSTER RS et al. Retroperitoneal lymphadenectomy for clinical stage A testic cancer (1965 to 1989): modification of technique and impact on ejaculation. J Urol 1993; 149: 237–243.

[34] HAHN NM, SWEENEY CJ. Germ cell tumors: an update of recent data and review of active protocols in stage I and metastatic disease. Urol Oncol 2005; 23: 293–302.

[35] STEPHENSON AJ, SHEINFELD J. The role of retroperitoneal lymph node dissection in the management of testicular cancer. Urologic Oncol 2004; 22: 225–235.

[36] FOSTER RS, BANIEL J, LEIBOVITCH I et al. Teratoma in the orchiectomy specimen and volume of metastasis are predictors of retroperitoneal teratoma in low stage nonseminomatous testis cancer. J Urol 1996; 155: 1943–1945.

[37] HERMANS BP, SWEENEY CJ, FOSTER RS et al. Risk of systemic metastases in clinical stage I nonseminoma germ cell testis tumor managed by retroperitoneal lymph node dissection. J Urol 2000; 163: 1721–1724.

[38] BANIEL J, FOSTER RS, EINHORN LH et al. Late relapse of clinical stage I testicular cancer. J Urol 1995; 154: 1370–1732.

[39] BANIEL J, FOSTER RS, ROWLAND RG et al. Complication of primary retroperitoneal lymph node dissection. J Urol 1994; 152: 424–427.

[40] JANETSCHEK G, HOBISCH A, PESCHEL R et al. Laparoscopic retroperitoneal lymph node dissection. Urology 2000; 55: 136–140.

[41] SPERMON JR, ROELEVELD TA, POEL van der HG et al. Comparison of surveillance and retroperitoneal lymph node dissection in stage I nonseminomatous germ cell tumors. Urology 2002; 59: 923–929.

[42] SPERMON JR, HOFFMANN AL, HORENBLAS S et al. The efficacy of different follow-up strategies in clinical stage I non-seminomatous germ cell cancer: a Markov simulation study. Eur Urol 2005; 48: 258–268.

[43] KLEPP O, DAHL O, FLODGREN P et al. Risk-adapted treatment of clinical stage I non-seminoma testis cancer. Eur J Cancer 1997; 33: 1038–1044.

[44] SCHMOLL H-J, SOUCHON R, KREGE S et al. European consensus on diagnosis and treatment of germ cell cancer: a report of the European germ cell cancer consensus group (EGCCCG). Ann Oncol 2004; 15: 1377–1399.

[45] JACOBSEN KD, THEODORSEN L, FOSSA SD. Spermatogenesis after unilateral orchiectomy for testicular cancer in patients following surveillance policy. J Urol 2001; 165: 93–96.

[46] JONKER-POOL G, van BASTEN JP, HOEKSTRA HJ et al. Sexual functioning after treatment for testicular cancer: comparison of treatment modalities. Cancer 1997; 80: 454–464.

[47] BÖHLEN D, BURKHARD FC, MILLS R et al. Fertility and sexual function following orchiectomy and 2 cycles of chemotherapy for stage I high risk nonseminomatous germ cell cancer. J Urol 2001; 165: 441–444.

[48] LANGENSTROER P, ROSEN MA, GRIEBLING TL et al. Ejaculatory function in stage T1 nonseminomatous germ cell tumors: retroperitoneal lymph node dissection versus surveillance – a decision analysis. J Urol, 2002; 168: 1396–1401.