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ORIGINAL ARTICLE

Germ cell testicular tumors in clinical stage A and normal values of serum tumor markers post-orchiectomy: the experience in the management of 300 consecutive patients

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Summary

Purpose: *To report the outcome and survival of patients with clinical stage A (CS-A) testicular seminoma (TS) treated with adjuvant carboplatin (CBDCA), and the value of primary nerve-sparing retroperitoneal lymphadenectomy (RPLA), adjuvant cisplatin and surveillance in the risk-adapted management of CS-A patients with nonseminomatous testicular tumors (NSTT) and normal values of serum tumor markers post-orchiectomy.*

Patients and methods: *From August 1985 to June 2003, 300 patients with CS-A germ cell testicular tumors (GCTT) entered a prospective non-randomized study. 163 patients with TS received post-orchiectomy 2 cycles of adjuvant CBDCA (400 mg/m^2 q 3 wks). 137 patients with NSTT were divided into two groups according to risk-adapted management: arm A (n=33)- RPLA in 23 high-risk patients (pre-orchiectomy AFP > 80 ng/ml, > 80% embryonal carcinoma, microvascular tumor invasion/VI$^+$), and in 10 low-risk patients; and arm B (n=104)-65 high-risk patients received 2 cycles of cisplatin-based chemotherapy, whereas 39 patients with low risk were put under surveillance.*

Results: *After a median follow-up of 4 years (range 1-9) all patients with TS were alive and disease-free (ADF). Relapses occurred in 3 (1.9%) patients treated with CBDCA, with complete response (CR) following cisplatin-based chemotherapy. Arm A relapses following RPLA in high-risk pathological stage (PS)- A occurred in 3 out of 18 (17%) patients, with CR following chemotherapy in 2 of them, while 5 patients with retroperitoneal lymph node (RPLN) metastasis had universal survival, resulting in 22 (95.6%) patients being ADF after a median follow-up of 9 years (range 8-10.2). Among 10 low-risk patients, 2 (20%) had RPLN metastasis and received cisplatin-based chemotherapy without disease relapse. All 10 patients are ADF after a median follow-up of 8.8 years (range 6.7-10.4). In arm B one of 65 high-risk patients (1.5%) treated with cisplatin-based chemotherapy relapsed in the lung at 9 months. Sixty-four (98.5%) patients are ADF after a median follow-up of 4 years (range 1.2-6.5). Six of 39 patients (15.4%) on surveillance relapsed and achieved CR with subsequent chemotherapy alone. All of them are ADF after a median follow-up of 5.5 years (range 1-10.2).*

Conclusion: *Adjuvant CBDCA chemotherapy is an acceptable approach in CS-A TS, whereas 2 cycles of cisplatin-based chemotherapy compare well with the results taken with RPLA in high-risk CS-A NSTT. Surveillance is an appropriate strategy in strictly selected patients with low-risk CS-A NSTT and normal post-orchiectomy values of serum tumor markers.*

Key words: chemotherapy, nonseminomatous testicular tumors, retroperitoneal lymphadenectomy, seminomatous testicular tumors, stage A, surveillance

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Introduction

Although adjuvant radiation to RPLN represents the standard treatment in CS-A TS, promising results have been reported with adjuvant CBDCA chemotherapy.

For the adjuvant management of CS-A NSTT the following options are available: RPLA, cisplatin-based chemotherapy and surveillance. It has been previously reported that CS-A NSTT patients who had undergone

RPLA were more likely to relapse if their pre-orchiectomy AFP was > 80 ng/ml, if they had > 80% embryonal carcinoma, or if VI^+ was present [1].

This study presents our experience during the past 10 years in the treatment of a large number of consecutive patients by various therapeutic approaches, having always in mind that evaluation of the data regarding relapse, survival, potential side effects and late events must be evaluated using comparative groups. The results of the present study permit a firm conclusion regarding this approach.

Patients and methods

Eligibility

CS-A NSTT was defined by the absence of clinically metastatic disease, normal ultrasound and CT scans of the abdomen/chest, including serum tumors markers (AFP, β-HCG, LDH). All patients with TS had normal AFP values. When elevated pre-orchiectomy, serum tumor markers had to be decreased to normal values after orchiectomy, according to their natural half-life.

Adjuvant chemotherapy in TS (February 1997-June 2003; n=163)

Post-orchiectomy the patients received 2 cycles of outpatient CBDCA chemotherapy with 400 mg/m^2 flat dose as 2 h infusion every 3 weeks, with antiemetic therapy (ondansetron 8 mg i.v.) before CBDCA administration.

Nerve-sparing RPLA in NSTT (with 2 cycles of cisplatin-based chemotherapy in PS-B1/B2; January 1994 -September 1997; n=33)

Twenty-three high-risk and 10 low-risk patients (without the previously mentioned criteria) were subjected to nerve-sparing RPLA.

Adjuvant chemotherapy in high-risk NSTT (PVB/PEBx2; February 1994-April 2003; n=65)

Adjuvant chemotherapy consisted of 2 cycles of PVB in 15 patients until December 1997; after that date 2 cycles of PEB were administered in the remaining 50 patients. PVB consisted of cisplatin 20 mg/m^2/d, d1-5, vinblastine 0.10 mg/kg/d, d1-2 and bleomycin 30mg i.m. d2, 9 and 16. PEB consisted of cisplatin 20 mg/m^2/d, d1-5, etoposide 100/m^2/d, d1-5 and bleomycin 30 mg i.m. d2, 9 and 16. The second cycle was given on day 21. Chemotherapy was postponed if the absolute neutrophil count (ANC) was < 1.5×10^9/l and/or platelet count <100×10^9/l, until marrow recovery.

Surveillance schedule in low-risk NSTT (August 1985-May 2003; n=39)

We slightly enlarged the total number of patients including some cases managed before 1994. Exclusion criteria included: pre-orchiectomy AFP > 80 ng/ml and/or β-HCG > 100 mIU/ml, >40% embryonal carcinoma, VI^+, locally advanced stage with invasion of rete testis. Patients on surveillance were followed-up monthly in the first year, every 2 months in the second year, 4 times in the third year, twice a year in the fourth and fifth year, with clinical examination, serum tumor markers estimation, chest x-ray and abdominal ultrasonography at each visit. CT of the chest and abdomen was done every 3 months in the first year and twice a year in the second year.

Assessment of toxicity

Acute toxicity, including ototoxicity and neurotoxicity, was evaluated according to the World Health Organization toxicity grading system [2].

Follow-up schedule

Patients with NSTT managed with primary RPLA and cisplatin-based chemotherapy were strictly followed-up monthly in the first year, every 2 months in the second year, every 3 months in the third year, twice a year in the fourth and fifth year, including physical examination, serum tumor markers estimation, chest x-ray, and abdominopelvic and scrotal ultrasonography at each visit. Abdominal CT was carried out every 4 months in the first year, and twice a year in the second year. Follow-up for TS patients was slightly different during the first 3 years of this study: every 2 months in the first year, every 3 months in the second year and every 4 months in the third year. Follow-up time was calculated from the date of orchiectomy.

Results

Patient characteristics

From August 1985 to June 2003 300 patients with GCTT entered prospectively this non-randomized study. The median age at orchiectomy was 28 years (range 16-54). Among 163 CS-A TS patients,

33 (20.2%) had elevated β-HCG before orchiectomy (mean 72.3 mIU/ml, range 5.18-800) and 45 (27.6%) elevated LDH (mean 470 IU/L, range 340-790). Pathologically locally advanced stage (PT2-T3) occurred in 47 (29.8%) patients and VI^+ in 45 (27.6%). Pathological and/or clinical risk factors at inclusion of 88 high-risk CS-A NSTT patients are presented in Table 1. Fifty-nine low-risk CS-A NSTT patients, managed with surveillance or RPLA, had not the previously mentioned criteria of the high-risk group.

Follow-up and survival

After a median follow-up of 4 years (range 1-9) all TS patients managed with adjuvant CBDCA chemotherapy are ADF. Relapse occurred in 3 (1.9%) patients within a median disease-free interval (MDFI) of 12 months (range 4-28). The relapses were localized in the RPLN and supraclavicular lymph nodes and lung (n=1), RPLN (n=1), and as only elevated values of β-HCG (n=1). All relapsing patients achieved CR with cisplatin-based chemotherapy. Two patients (0.7%) developed tumor in the contralateral testis at 33 and 36 months after completion of adjuvant CBDCA chemotherapy (1 seminoma, 1 nonseminoma).

Relapses following RPLA in high-risk PS-A NSTT occurred in 3 of 18 (17%) patients within a MDFI of 6.3 months (range 2-12), with CR following chemotherapy in 2 of them. One patient died due to widespread metastatic disease despite salvage chemotherapy and surgery of lung metastasis. All 5 patients in the high-risk group with nodal metastasis had universal survival. ADF are 22 (95.6%) patients after a median follow-up of 9 years (range 8-10.2). Among 10 low-risk patients managed with RPLA, only 2 (20%) with positive lymph nodes received cisplatin-based chemotherapy, whereas the relapse rate was zero. All patients are ADF after a median follow-up of 8.8 years (range 6.7-10.4). There was strong but not statistically significant difference regarding the relapse rate and survival in favor of high-risk PS-A patients, whereas the survival in PS-B1 was universal in both groups. Eight of 23 (34.8%) high-risk patients necessitated cisplatin-based chemotherapy following RPLA (3 in relapse and 5 due to nodal metastasis) *versus* 2 of 10 patients with nodal metastasis in the low-risk group of patients. The benefit from RPLA was 65% in the high-risk and 80% in the low-risk group of patients (Table 2).

One high-risk patient managed with 2 cycles of PEB relapsed in the lung at 9 months and died despite salvage chemotherapy and surgery. ADF are 64 (98.5%) patients for a median follow-up of 48 months (range 14-78). One (0.3%) patient developed a metachronous CS-A TS 4 months after completion of 2 cycles of cisplatin-based chemotherapy and was put under surveillance.

Six of 39 (15.4%) patients on surveillance relapsed after a median follow-up of 6.7 months (range 3-10) in the lung (n=1), RPLN (n=3) and as only elevated values of serum tumor markers (n=2). All relapses occurred within the first year. Lung metastasis occurred earlier than those in the RPLN (3 and 4.5 months, respectively). RPLN relapses were detected in half of the relapsing patients. Serum tumor markers elevation preceded radiographic demonstration of

Table 1. Risk factors in high-risk CS-A NSTT patients at inclusion

Risk factor	*RPLA (n=23) n (%)*	*PVB/PEB×2 (n=65) n (%)*
> 80% embryonal carcinoma	11 (47.8)	33 (50.8)
VI+	13 (56.5)	38 (58.5)
AFP > 80 ng/ml	7 (30.4)	9 (13.8)
2 risk factors	7 (30.4)	20 (30.8)
RPLN metastasis	5 (20.8)	–

For abbreviations see text

Table 2. Risk-adapted management in CS-A/PS-A and B1 NSTT: primary nerve sparing RPLA (n=33)

	High risk n (%)	*Low risk n (%)*
PS-A	18	8
Relapse	3 (17)	–
Median relapse-free interval, months (range)	6.3 (2-12)	–
Location of metastasis		–
Lung	2	
RPLN	1	
CR following CT in relapse	2 (66.6)	–
Alive, disease-free	17 (94.4)	8 (100)
Median follow-up, years (range)	9 (8-10.2)	8.9 (6.7-10.4)
PS-B1	5	2
Relapse	–	–
Median follow-up, years (range)	9.25 (8-10.2)	8.5 (7.3-9.25)
PS – A +B1	23	10
Relapse	3 (13)	–
CR after relapse	2 (66.6)	–
Alive, disease-free	22 (95.6)	10 (100)
Median follow up, years (range)	9 (8-10.2)	8.8 (6.7-10.4)

For abbreviations see text

Table 3. CS-A GCTT with normal serum tumor markers values following orchiectomy: accumulated results of the applied therapeutic approach (n=300)

Histology	*Therapeutic regimen*	*Patients n*	*Relapse n (%)*	*Alive, disease-free n (%)*
Seminoma	Chemotherapy (CBDCAx2)	163	3 (1.8)	163 (100)
Non-seminoma	"Low risk" surveillance	39	6 (15.4)	39 (100)
	"High risk" chemotherapy (PVB/PVB×2)	65	1 (1.5)	64 (98.5)
	"Low risk" RPLA	10	–	10 (100)
	"High risk" RPLA	23	3 (13)	22 (95.6)
Subtotal non-seminoma		137	13 (9.5)	135 (98.5)
Total		300	16 (5.3)	298 (99.3)

For abbreviations see text

metastasis in 3 (50%) patients, and in 2 (33%) patients it was the only sign of relapse. All relapsing patients presented with low clinical stage and achieved CR with chemotherapy alone. All 39 patients are ADF after a median follow-up of 5.5 years (range 1-10.2). Two (5.1%) patients developed metachronous CS-A testicular tumor at 54 and 111 months (1 seminoma, 1 nonseminoma) and were managed with only strict follow-up after orchiectomy.

Cumulative comparative analysis of the therapeutic results in the TS *versus* the NSTT group demonstrated relapse rate of 1.8 *versus* 9.5% ($p < 0.05$) and survival of 100 *versus* 98.5% ($p > 0.05$), respectively. Analysis within the NSTT group demonstrated less frequent relapse rate in the high-risk group of patients managed with 2 cycles of cisplatin-based chemotherapy, whereas 2 patients died following RPLA and chemotherapy, respectively. In the low-risk group of patients the relapse rate was lower, favoring patients managed with RPLA, whereas the survival was identical in both groups. Of the total number of 300 patients with germ-cell testicular tumors in CS-A, relapses occurred in 5.3% of the patients, whereas the survival rate achieved was 99.3% (Table 3).

Toxicity and postoperative complications

Besides mild gastrointestinal discomfort, adjuvant CBDCA chemotherapy was well-tolerated by all patients. In 131 treatment cycles with adjuvant CBDCA chemotherapy there were no life-threatening toxicities. Myelosuppression was minimal with no patient having grade 2-3 leukopenia and thrombocytopenia. No alopecia, renal, neuro- or ototoxicity were encountered. In 5 patients treated with cisplatin-based chemotherapy (PVB 2 patients, PEB 3 patients) the second cycle was delayed for more than 7 days, due to acute grade 3-4 neutropenia, necessitating G-CSF administration in 3 of them.

Table 4. Hematological toxicity in 65 patients treated with 2 cycles of PVB (15 patients) or PEB (50 patients) for high risk CS-A NSTT

	PVB	*PEB*
Number of cycles	31	100
Grade 3-4 neutropenia	8	19
Febrile neutropenia	1	4
Grade 2-3 thrombocytopenia	3	8

Table 5. Risk-adapted management in CS-A NSTT: primary nerve sparing RPLA complications

Complication	*Intraoperative*	*Postoperative*	
		Early (patients, n)	*Late (patients, n)*
Surgical	–	Mechanical ileus (1) Paralytic ileus (1) Wound infection (1) Gastric bleeding (1)	Ventral hernia (1) Ejaculatory disturbances (4)
Medical	–	Pneumonia+icterus (1)	–

No patient required platelet transfusion (Table 4). Non-hematological side effects such as renal toxicity, neurotoxicity, ototoxicity and alopecia were not observed. Two patients developed tinitus. No bleomycin-induced lung fibrosis or other late sequels (i.e. secondary leukemia, major cardiac events and high blood pressure) were observed.

There were 2 minor and 4 major complications in 3 (9.1%) patients following RPLA. The most prominent postoperative complication was mechanical ileus in l patient necessitating repeat laparotomy and lysis of adhesions. Ejaculatory disturbances occurred in 4 (12.1%) patients, all with left-sided testicular tumor. Therefore, RPLA was technically more difficult regarding preservation of ejaculatory potency for left-sided testicular tumors (Table 5).

Discussion

We recently reported on the survey of 444 CS-A TS patients that adjuvant CBDCA chemotherapy is superior compared to radiotherapy, having in view relapse and survival rates, simplicity and duration of treatment, acute/chronic side effects and late events in the sense of second malignancy and bilateral testicular tumors [3]. Overuse of radiation had been linked to the development of gastrointestinal disorders, infertility, secondary cancers and leukemia, and yet there was still a 5% risk of relapse. Surveillance alone will save the patients the risk of adverse effects, and at the same time their risk of relapse will only increase up to 15%. Of 431 men with CS-A TS, 203 were managed by surveillance following orchiectomy. By the end of 9.2 years of follow-up, 35 (17.2%) men had relapsed, 5 (2.5%) of them more than 5 years after their orchiectomy. The actuarial risk of relapse at 5 and 10 years was 15% and 18%, respectively. The actuarial risk of relapse between 5 and 10 years was 4%. These results demonstrate that there is a small but clinically significant risk of relapse more than 5 years after orchiectomy for CS-A TS. These data support the need for long term surveillance [4]. Adjuvant CBDCA chemotherapy has not yet been studied to any significant degree among patients with CS-A TS regarding the occurrence of late events.

RPLA is considered gold standard in CS-A NSTT by most US authors, as this approach has shown long-term efficacy in 98% of the patients. In experienced hands, RPLA ensures optimal staging of the disease with minimal morbidity and reduces the risk of RPLN progression and the need for frequent CT scans during follow-up [5]. However, even in PS-A, up to 10% of patients develop metastasis outside the retroperitoneum (17% in high-risk PS-A patients in our study), with, as expected, a higher figure (25%) in CS-B patients. A randomized study conducted by the Testis Intergroup demonstrated that 2 cycles of adjunctive cisplatin-based chemotherapy decreased, or, according to our experience, eliminated completely the risk of metastatic progression [6]. Surgical series highlighted the central role of VI^+ in the extension of CS-A disease and in the metastatic evaluation of PS-A [7,8]. In addition to VI^+, the presence of embryonal carcinoma in the orchiectomy specimen was shown to be associated with higher risk of systemic recurrence [9]. Both observations were confirmed in our study.

Twenty years ago, the high cure rate of advanced disease by cisplatin-based chemotherapy led to the introduction of surveillance as an alternative to surgery. This methodology resulted in 30% of the patients developing metastatic disease and requiring chemotherapy. Long term follow-up studies were similar to those reported in RPLA series, which confirmed surveillance as a valid strategy. In 1987, VI^+, presence of embryonal carcinoma, and absence of yolk sac were stratified into a prognostic index. The clinical relevance of this index was prospectively validated, as illustrated by a 47% relapse rate in the high-risk group defined by the combination of any three risk factors. Patients without risk factors, defined as low-risk, had on surveillance a relapse rate of 15.4%, as in the reported study, showing that they really harbored low-volume metastatic disease and were cured with only cisplatin-based chemotherapy without adjunctive surgery [10].

Having identified the patient subset at risk of developing metastatic disease, the next logical step, in view of the high efficacy of cisplatin-based chemotherapy in metastatic NSTT, was adjuvant chemotherapy. Several variations of adjuvant PEB regimen, i.e. number of cycles and total dose of etoposide, have been reported [11-14]. No clear improvement in efficacy was obtained with 3 cycles of PEB or 500 mg/m^2 of etoposide per cycle, as compared to 2 cycles with 360 mg/m^2 of etoposide per cycle. A recent study demonstrated absence of relapse and minimal toxicity without late side effects, suggesting that 2 cycles of PEB with 360 mg/m^2 of etoposide were both effective and well tolerated. The expected relapse rate was 1.9%, with median disease-free interval of 9 months (similar figures were observed in the present study). No relapse occurred later than 27 months after diagnosis. Those who relapsed with viable tumor did so at an earlier time than those with mature teratoma (7 *versus* 22 months) and remained refractory to further chemotherapy [15].

However, there is some concern with the administration of PEB: 1) second malignancy, mainly secondary leukemia, but also adenocarcinomas and sarcomas; 2) development of chemorefractory metastatic disease necessitating salvage chemotherapy and surgery (the prognosis of those patients according to our experience is particularly worse); 3) development of relapse in the sense of mature teratoma, mainly in the retroperitoneum, resulting in the "teratoma growing syndrome", calling for RPLA; 4) long- term cardiovascular toxicity. Except the isolated case of relapsing chemoresistant metastatic disease with fatal outcome, none of the mentioned hazards were observed in the present study, based only on 2 cycles of chemotherapy.

Several studies confirmed the absence of impact of 2 cycles of cisplatin-based and CBDCA chemotherapy on sperm characteristics [11,12,15]. However, systemic chemotherapy has significant impact on the contralateral testis regarding the development of metachronous germ-cell tumors in comparison to patients who were under surveillance (1.2-1.4 *versus* 5.12%; $p < 0.05$) [16].

In conclusion, adjuvant CBDCA chemotherapy is an acceptable approach in CS-A TS: application is easy and of short duration, side effects are mild and relapse rate is lower than after irradiation. However, adjuvant CBDCA chemotherapy necessitates long term follow-up in order to determine more precisely late events. Patients with CS-A NSTT are not necessarily helped by initial RPLA except to secure the retroperitoneum and make the diagnosis of relapse potentially easier, but at what price? According to our experience, 2 cycles of PEB with reduction of etoposide total dose (360 mg/m^2/cycle) constitute an effective treatment with mild toxicity for high risk patients, whereas surveillance is an acceptable method in strictly selected patients with low risk CS-A NSTT and normal values of serum tumor markers following orchiectomy. In view of the reported long-term toxicities of testicular cancer treatment, it is of utmost importance to continuously optimize the management of low-stage testicular germ-cell tumors in order to limit treatment-associated side effects.

References

1. Heidenreich A, Sesterhenn IA, Mostofi FK et al. Prognostic risk factors that identify patients with clinical stage I nonseminomatous germ cell tumors at low risk and high risk for metastasis. Cancer 1998; 83: 1002-1011.
2. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.
3. Argirovic Dj, Radosevic - Jelic Lj. Carboplatin (CBDCA) monochemotherapy (MCHT) versus radiotherapy (Rtx) in clinical stage A (CS-A) seminomatous testicular tumors (STT): the two institutions experience. BJU Int 2004 (Suppl); 34: 115 (abstr).
4. Chung P, Parker C, Panzarella T et al. Surveillance in stage I testicular seminoma - risk of late relapse. Can J Urol 2002; 9: 1637-1640.
5. Foster RS, Donohue JP. Retroperitoneal lymph node dissection for the management of clinical stage I nonseminoma. J Urol 2000; 163: 1788-1792.
6. Willians SD, Stablein DM, Einhorn L et al. Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. N Engl J Med 1987; 317: 1433-1438.
7. Albers P, Siener R, Kliesch S 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: 1505-1512.
8. Hermans BP, Sweeney CJ, Foster RS et al. Risk of systemic metastases in clinical stage I nonseminoma germ cell testis tumors managed by retroperitoneal lymph node dissection. J Urol 2000; 163: 1721-1724.
9. Sweeney CJ, Hermans BP, Heilman DK et al. Results and outcome of retroperitoneal lymph node dissection for clinical stage I embryonal carcinoma- predominant testis cancer. J Clin Oncol 2000; 18: 358-362.
10. Freedman LS, Parkinson MC, Jones WG et al. Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. Lancet 1987; 2: 294-298.
11. Studer UE, Fey MF, Calderoni A, Kraft R, Mazzucchelli L, Sonntag RW. Adjuvant chemotherapy after orchiectomy in high-risk patients with clinical stage I non-seminomatous testicular cancer. Eur Urol 1993; 23: 444-449.
12. Cullen MH, Stenning SP, Parkinson MC et al. Short-course adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: a Medical Research Council report. J Clin Oncol 1996; 14: 441-448.
13. 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.
14. Pont J, Albrecht W, Postner, G, Sellner F, Angel K, Holtl 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- 448.
15. Chevreau CH, Mazerolles C, Soulie M 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: 209-215.
16. Sonneveld DJ, Schaffordt Koops H, Sleijfer DT, Hoekstra HJ. Bilateral testicular germ cell tumours in patients with initial stage I disease: prevalence and prognosis - a single centre 30 years experience. Eur J Cancer 1998; 33: 244-252.