PERGAMON

European Journal of Cancer 37 (2001) 576–582

European Journal of Cancer

www.ejconline.com

Stage I non-seminomatous germ-cell tumours of the testis: identification of a subgroup of patients with a very low risk of relapse

J. Alexandre [a], K. Fizazi [a,*], C. Mahé [b], S. Culine [c], J.-P. Droz [d], C. Théodore [a], M.-J. Terrier-Lacombe [e]

[a] *Department of Medicine, Institut Gustave Roussy, 94805 Villejuif cedex, France*
[b] *Department of Biostatistics, Institut Gustave Roussy, 94805 Villejuif cedex, France*
[c] *Department of Medicine, centre Val d'Aurelle, Montpellier, France*
[d] *Department of Medicine, centre Léon Berard, Lyon, France*
[e] *Department of Pathology, Institut Gustave Roussy, 94805 Villejuif cedex, France*

Received 10 July 2000; received in revised form 31 October 2000; accepted 7 December 2000

Abstract

There is no consensus about a reproducible prognostic model capable of distinguishing between clinical stage I non-seminomatous germ cell tumour (NSGCT) carrying a high and low risk of relapse. The aim of this study was to assess the prognostic value of histological parameters in patients with stage I NSGCT undergoing surveillance after orchiectomy. We retrospectively evaluated tumour specimens from 88 consecutive stage I NSGCT patients undergoing surveillance in our institution between 1984 and 1996. 24 patients relapsed (27%). Multivariate analysis singled out vessel invasion (VI) (relative risk (RR) = 3.8; 95% confidence interval (CI) 1.4–10.4) and the presence of mature teratoma (RR = 0.2; 95% CI 0.1–0.6) as independently correlated with relapse-free survival (RFS). Patients can be classified accordingly into three prognostic groups with a low (27 patients with mature teratoma but without VI), intermediate (34 patients with both VI and mature teratoma or with neither VI or mature teratoma) and a high risk (23 patients with VI, but without mature teratoma) of relapse. Relapse rates in these three groups were 0%, 29% (95% CI: 23–35%) and 61% (95% CI: 55–67%), respectively. This prognostic index, based on two standard pathological parameters, identified a subgroup with a very low risk of relapse that represents approximately one third of stage I patients. Patients who belong to this subgroup should be managed by surveillance only, instead of retroperitoneal lymph node dissection (RPLND) or adjuvant chemotherapy.

Keywords: Embryonal carcinoma; Non-seminomatous germ-cell tumour; Prognostic factors; Stage I; Teratoma; Vascular invasion

1. Introduction

In 50% of patients, testicular non-seminomatous germ-cell tumour (NSGCT) is confined clinically to the testis, epididymis or spermatic cord at initial diagnosis, this being the definition of stage I disease [1]. In most European countries, three therapeutic options are now considered appropriate in clinical stage I disease after orchiectomy: nerve-sparing retroperitoneal lymph node dissection (RPLND) [2], adjuvant chemotherapy [3] and close surveillance [4]. With this latter 'wait and see' policy, approximately 30% of patients will relapse due to occult metastases [4]. Follow-up procedures including computed tomography (CT) scan and tumour marker measurements permit the diagnosis of small recurrent lesions that can be cured by cisplatin-based chemotherapy in virtually all cases [5]. Consequently, a 97% long-term disease-free survival (DFS) rate can be achieved with the surveillance approach [6,7], while avoiding immediate toxicity and the long-term sequelae of therapies in the majority of patients. However, the constraints that frequent CT scan examinations and marker determinations impose upon patients, which are compounded by the anxiety that the likelihood of a recurrence arouses, are significant limitations of the surveillance policy. Moreover, poor compliance with

* Corresponding author. Tel.: +33-1-4211-4301; fax: +33-1-4211-5230.
E-mail address: fizazi@igr.fr (K. Fizazi).

0959-8049/01/$ - see front matter
PII: S0959-8049(00)00442-1

follow-up can lead to poor-prognosis recurrent disease [8]. This is why many oncologists consider that patients at high risk of relapse should benefit from immediate treatment after orchiectomy consisting of RPLND [2] or adjuvant chemotherapy [3], both of which have been shown to yield disease-free survival rates of greater than 95% with no or limited sequelae.

Unfortunately, there is still no consensus about a reproducible, objective prognostic model capable of distinguishing between clinical stage I NSGCT carrying a high and low risk of relapse [9]. Histologically-proven blood and lymph vessel invasion (VI) of the primary tumour is recognised as the best independent predictive factor of relapse [2,4]. The presence of embryonal carcinoma (EC) in the primary tumour, the absence of teratoma and yolk sac tumour, a normal preoperative alpha-fetoprotein (AFP) level and the expression of Ki-67 were also shown to have a prognostic value in several studies ([5,9] for review). In a recent retrospective study, a prognostic index was designed for patients undergoing RPLND, based on the percentage of EC in the tumour and the presence of VI [10]. In the present study, we evaluated tumour specimens from patients undergoing surveillance after orchiectomy in our institution, for standard histopathological parameters and the percentage of EC. The objective was to individualise prognostic groups based on a multivariate analysis of relapse-free survival (RFS) in patients undergoing surveillance after orchiectomy.

2. Patients and methods

From 1984 to 1996, RPLND and surveillance have been used at the Institut Gustave Roussy to manage patients after orchiectomy for clinical stage I NSGCT. The choice between these two options was mainly based on the patient's preference and his potential ability to comply with the follow-up procedures, but not on the histopathological features of the primary testis tumour. Adjuvant chemotherapy was not routinely used.

Here we report the outcome of patients with clinical stage I NSGCT who underwent surveillance after orchiectomy at the Institut Gustave Roussy. Tumours were classified as clinical stage I disease if the CT scan of the chest, abdomen, and pelvis and serum tumour markers (i.e. AFP, total human chorionic gonadotrophin (HCG) and the beta subunit (βHCG)) were normal. Serum markers that were elevated before orchiectomy were expected to normalise postoperatively in accordance with their half-life. Close surveillance consisted of tumour marker measurements and a monthly clinical examination during the first year, then every 2 months during the second year, then every 4 months until the fifth year and twice a year thereafter. Thoracic and abdomino-pelvic CT scans were performed every 3 months during the first year, then twice a year until the fifth year and once a year thereafter.

Initial patient characteristics and outcomes were collected retrospectively from clinical records. Preoperative tumour marker levels were the last measurements obtained before orchiectomy (usually the day before). A single pathologist, who was blinded to the evolution of the disease, reviewed the haematoxylin and eosin (H&E) stained slides of the primary testis tumour. Each case was assessed meticulously to identify germ-cell tumour subtypes (embryonal carcinoma, seminoma, choriocarcinoma, yolk sac tumour, carcinoma *in situ*, mature and immature teratoma). The proportion of EC was based on the pathologist's general impression of the entire tumour specimen on the H&E-stained slides. She also assessed invasion of the tunica and cord vessels. The term 'vessel invasion' (VI) designates the presence of either venous or lymphatic invasion. VI was considered positive when a heap of tumour cells was found adhering to a vessel wall or when endothelial cells surrounded them.

RFS was the time between the orchiectomy and relapse. RFS curves were computed using the Kaplan–Meier method. Both univariate and multivariate analyses were used to assess prognostic factors. Age at orchiectomy, the percentage of EC and tumour marker levels were considered as dichotomous variables. The cut-offs used were the median value for the first two variables and the upper normal threshold for tumour markers. In the univariate analysis, RFS was compared using the log-rank test. The variables analysed were: age at orchiectomy, preoperative tumour marker levels (AFP, HCG, bHCG), histological features of the testis tumour including: the percentage of EC, the presence of VI, cord or tunica invasion, and each of the germ-cell tumour subtypes. Each variable associated with a P value lower than 0.10 in the univariate analysis was included in the multivariate analysis. The multivariate analysis of RFS was performed using the Cox's proportional hazards model. The P value used to retain variables in the final model was $P < 0.05$. A stepwise procedure was used. The P value associated with each relative risk (RR) was assessed using the Wald test. The relationship between the percentage of EC and the presence of VI was estimated using a non-parametric Wilcoxon rank sum test.

3. Results

3.1. Patient characteristics

Between 1 January 1984 and 31 December 1996, 88 consecutive patients with clinical stage I NSGCT underwent surveillance after orchiectomy at the Institut Gustave Roussy. During the same period, 71 patients

with clinical stage I disease underwent RPLND. The main characteristics of the 88 patients are listed in Table 1. At the time of the orchiectomy, the median age was 30.5 years (range 15.9–55.7 years). Histological slides were not available for review in 4 patients. Thus, the histolological features of the primary tumour were available for 84 patients. In 72 cases, we obtained all paraffin-embedded fixed tissue blocks, and analysed a range of 6–21 blocks per tumour. In 12 cases, only 1–6 H&E-stained slides were collected. 11 patients had pure EC and no pure choriocarcinoma was identified. The histological components of composite NSGCT were found in the following proportions: embryonal carcinoma (85%), mature teratoma (52%), immature teratoma (50%), yolk sac tumour (26%), choriocarcinoma (27%) and seminoma (36%). Vessel invasion was found in 40 patients (48%). Sufficient tunica and cord material was available for assessment in only 76 and 74 patients, respectively. Tunica and cord invasion was identified in 27 (36%) and 6 (8%) tumours, respectively.

Table 1
Patient characteristics

Characteristics	Patients	
	Number evaluated	Number (%)
Age at orchiectomy (years)	88	Median (range): 30.5 (15.9–55.7)
⩽30		44 (50)
>30		44 (50)
Preoperative tumour marker levels		
AFP (ui/ml)	74	
⩽10		29 (39)
>10		45 (61)
HCG (ui/ml)	62	
⩽10		39 (63)
>10		23 (37)
β-HCG (ui/ml)	57	
⩽0.1		35 (61)
>0.1		22 (39)
Pathology	84	
Embryonal carcinoma (EC) (%)		Median (range): 42.5 (0–100)
⩽40%		42 (50)
>40%		42 (50)
Choriocarcinoma		23 (27)
Yolk sac tumour		22 (26)
Seminoma		30 (36)
Mature teratoma		44 (52)
Immature teratoma		42 (50)
Carcinoma *in situ*		37 (44)
Vessel invasion		40 (48)
Cord invasion	74	6 (8)
Tunica invasion	76	27 (36)
Relapses	88	24 (27)
Elevated markers		18 (75)
Retroperitoneal nodes		14 (58)
Mediastinal nodes		3 (13)
Pulmonary metastases		3 (13)
IGCCCG classification		
Good prognosis		23 (96)
Intermediate prognosis		1 (4)
Chemotherapy[a]	24	24 (100)
4 EP or 3 BEP		18 (75)
4 BEP		5 (21)
Other regimens (including salvage)		4 (17)

AFP, alpha-fetoprotein; HCG, human chorionic gonadotrophin; BHCG, beta-human chorionic gonadotrophin; IGCCCG, International Germ-Cell Consensus Classification; (B)EP, (bleomycin), etoposide, cisplatin.

[a] Total higher than 100% because 2 patients received one and two salvage regimens, respectively.

3.2. Follow-up

By 1 May 1999, 24 of the 88 patients had relapsed (27%). The median follow-up of the 64 relapse-free patients was 4.3 years (range: 1–12 years). All relapse-free patients had been followed-up for at least 1 year and 89%, for at least 2 years. All relapses occurred before the second year after the orchiectomy and 21 of them (88%) within 12 months. One patient developed a pure seminoma in the controlateral testis 34 months after the primary tumour. This patient was considered recurrence-free in this analysis. All, except one relapse, were classified in the good-risk group according to the International Germ-Cell Consensus Classification [11]. Retroperitoneal nodes were the most frequent sites of relapse (14 patients). Pulmonary metastases were observed in 3 patients, but no extra-pulmonary visceral metastases occurred. Tumour markers were elevated in 18 patients (75%), 7 of whom (39%) had no clinical or radiological evidence of disease. Most patients (23 patients) were enrolled at relapse in a French multicentric study comparing four cycles of combination etoposide–cisplatin to three cycles of the etoposide–cisplatin–bleomycin regimen (BEP) in good-prognosis advanced NSGCT [12] or were routinely given three cycles of BEP. After a median time from relapse of 49 months (range: 1–117 months), all patients but 1 (96%) were alive and free of disease, including the 2 patients who had required salvage chemotherapy. One patient who developed a relapse of intermediate prognosis died suddenly of a pulmonary embolism a few days after the third cycle of chemotherapy.

During the same period (1 January 1984 and 31 December 1996), 28 of 71 patients (39%) with clinical stage I NSGCT who underwent RPLND were found to have pathological II disease.

3.3. Univariate analysis

According to the univariate analysis (Table 2), RFS was significantly lower in patients presenting VI (RR = 5.3; 95% confidence interval (CI) 2.0–14.2), cord invasion (RR = 3.8) or a percentage of EC > 40% (RR = 3.5;

95% CI 1.4–8.7) in the testis tumour. The presence of mature teratoma (RR = 0.2; 95% CI 0.1–0.5) and of immature teratoma (RR = 0.4; 95% CI 0.1–0.8) was significantly correlated with a longer RFS. Neither age at orchiectomy, nor preoperative tumour marker levels was significantly associated with the risk of relapse.

3.4. Multivariate analysis

In the multivariate analysis, only two factors were independently correlated with RFS: VI, which was associated with a higher probability of relapse (RR = 3.8; 95% CI 1.4–10.4) and the presence of mature

Table 2
Univariate and multivariate analysis of relapse-free survival (RFS)

Variable	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Vessel invasion (VI)		< 0.001		0.008
Yes	5.3 (2.0–14.2)		3.8 (1.4–10.4)	
No	1		1	
Mature teratoma		0.001		0.005
Yes	0.2 (0.1–0.5)		0.2 (0.1–0.6)	
No	1		1	
Embryonal carcinoma (EC) (%)		0.008		NS
⩽40	1			
> 40	3.5 (1.4–8.7)			
Cord invasion		0.02		NS
Yes	3.8 (1.3–11.2)			
No	1			
Immature teratoma		0.02		NS
Yes	0.4 (0.1–0.8)			
No	1			
Seminoma		0.3	NI	
Yes	0.6 (0.2–1.5)			
No	1			
Yolk sac tumour		0.4	NI	
Yes	1.5 (0.6–3.5)			
No	1			
Preoperative HCG level		0.4	NI	
⩽10 ui/ml	1			
> 10 ui/ml	1.4 (0.6–3.8)			
Tunica invasion		0.5	NI	
Yes	1.3 (0.6–3.2)			
No	1			
Age at orchiectomy (years)		0.6	NI	
⩽30	1			
< 30	0.8 (0.4–1.8)			
Preoperative AFP level		0.7	NI	
⩽10 ui/ml	1			
> 0 ui/ml	1.2 (0.5–2.8)			
Choriocarcinoma		0.7	NI	
Yes	0.9 (0.3–2.2)			
No	1			
Carcinoma *in situ*		0.7	NI	
Yes	0.9 (0.4–2.0)			
No	1			
Preoperative β-HCG level		0.9	NI	
⩽0.1 ui/ml	1			
> 0.1 ui/ml	0.9 (0.3–2.7)			

AFP, alpha-fetoprotein; HCG, human chorionic gonadotrophin; BHCG, beta-human chorionic gonadotrophin; RR, relative risk; CI, confidence interval; NS, non-significant; NI, not included in the multivariate model. 1 = reference group.

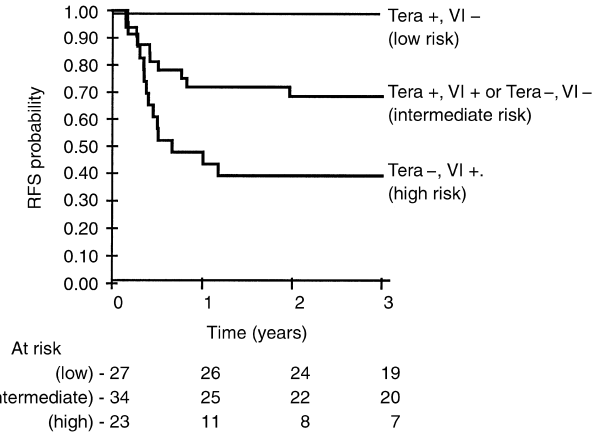

Fig. 1. Probability of relapse-free survival (RFS) according to our prognostic model (VI, vessel invasion; tera, mature teratoma).

teratoma which was associated with a lower probability of relapse (RR = 0.2; 95% CI 0.1–0.6) (Table 2). The results of the statistical analysis were not significantly modified when the percentage of EC was considered as a continuous variable, nor when the EC cut-off value was fixed at 80%, as in a previous study [10] (data not shown). Likewise, the presence of teratoma remained an independent prognostic factor when mature and immature subtypes were pooled ($P < 0.001$). The fact that the percentage of EC ceased to be associated with RFS in the multivariate analysis could be explained by the significant correlation found between this parameter and VI ($P = 0.008$, Wilcoxon test). Indeed, the median percentage of EC was 60 and 20% in 40 (range: 0–100%) tumours with, and 44 (range: 0–100%) without VI, respectively.

Using the two independent prognostic factors, patients can be divided into three well-balanced groups classified as having a low, intermediate and high risk of relapse, respectively (Fig. 1). 27 patients (32%) with mature teratoma, but no VI were classified in the very low-risk group, since none of them has relapsed. 23 patients (27%) with VI and no mature teratoma were classified in the high risk group since 14 of them have relapsed (61%, 95% CI: 55–67%). Among the 34 patients (40%) with both VI and mature teratoma or with neither VI nor mature teratoma, 10 patients have relapsed (29%, 95% CI 23–35%).

4. Discussion

In agreement with previous studies, we report recurrences in 27% of patients with clinical stage I NSGCT who underwent surveillance after orchiectomy [4,6,7,13]. The percentage of pathological stage II disease among stage I patients who underwent RPLND was also similar to previous reports [10,14]. In fact, the choice of a 'wait and see' policy after orchidectomy for clinical stage I disease, rather than RPLND was not based on prognostic factors evaluation, but mainly on the patient's preference. Therefore, we can assumed that our patients cohort is representative of the stage I NSGCT population, regarding the risk of relapse and histological parameters.

Vessel invasion by the tumour has been identified as the most important predictive factor of occult metastatic disease in clinical stage I patients in our study, and this is in agreement with most published studies [2,4,6,7,10,13–18] (Table 3). Whereas, lymphatic and venous invasion were distinguished in early reports [4], it is now considered acceptable to pool these parameters not only because the differential diagnosis is difficult for

Table 3
Summary of studies assessing independent prognostic factors by multivariate analysis for occult metastatic disease in clinical stage I NSGCT patients

Studies (references)	No. of patients	End point	Study methodology	Multivariate analysis of prognostic factors			
				VI	EC	No teratoma	No YST
2	279	Pathological	Retrospective	Yes	No	Yes	Yes
10	149	stage II	Retrospective	Yes	Yes†	ND	ND
14	92	disease	Retrospective	Yes	Yes†	No	No
17	78	in patients	Retrospective	Yes	Yes†	No	No
18	320	undergoing	Retrospective	Yes	Yes*	ND	ND
16	482	RPLND	Prospective	Yes	No	No	No
4	259	Relapse	Retrospective	Yes	Yes	ND	Yes
6	373	in patients	Prospective	Yes	Yes	No	Yes
7	105	undergoing	Prospective	Yes	Yes*	No	No
13	154	surveillance	Prospective	Yes	No	No	No
Present study	84		Retrospective	Yes	No	Yes	No

AFP, alpha-fetoprotein; HCG, human chorionic gonadotrophin; BHCG, beta-human chorionic gonadotrophin; IGCCCG, International Germ-Cell Consensus Classification; NS GCT, non-seminomatous germ cell tumour; ND, not determined; VI, presence of vessel invasion; EC, presence of embryonnal carcinoma subtype (qualitative assessment); EC*, predominance of EC subtype (semi-quantitative assessment); EC†, high percentage of EC (quantitative assessment); YST, yolk sac tumour subtype; RPLND, retroperitoneal lymph node dissection.

the pathologist, but also because lymphatic and venous invasion are consistently correlated [6]. However, identification of VI is a difficult task requiring meticulous scrutiny of blocks by an experienced pathologist [16]. Consequently, the validity of VI as a prognostic factor is not foolproof for the management of patients outside tertiary referral cancer centres. Future prospective studies should include independent reviews of pathological slides by several pathologists from both primary hospital and tertiary referral centres.

Using multivariate analysis, several retrospective studies singled out the proportion of EC as an independent factor predictive of the pathological stage in patients submitted to RPLND [10,14,17,18] (Table 3), but this was not corroborated by the large multicentre prospective study of the Testicular Cancer Intergroup [16]. Two large prospective studies, in which EC was used as a qualitative variable (i.e. presence or absence), demonstrated conflicting results in patients who underwent surveillance [6,13]. However, qualitative assessment of EC is purported to underestimate the prognostic value of EC [19]. Predominant EC histology (i.e. no more than a microscopic focus of an accompanying subtype) was recently identified as an independent prognostic factor for relapse among 105 patients undergoing surveillance [7]. To our knowledge, no study has assessed the prognostic value of the percentage of EC in patients undergoing surveillance after orchiectomy. In the present study, patients with a percentage of EC > 40% relapsed more frequently than the others did. However, the percentage of EC was not found to be an independent prognostic factor after adjustment for VI and the presence of mature teratoma in the multivariate analysis. The percentage of EC and VI seemed to be strongly interrelated in our study, and this is in agreement with previous reports which showed that EC was the invading element in > 90% of VI [16,20].

Three studies have already demonstrated that the presence of teratoma elements in the primary tumour is a favourable prognostic factor in patients with clinical stage I disease [2,21,22]. Indeed, among 279 patients submitted to RPLND, the presence of teratoma was associated with pathological stage I disease and a lower risk of relapse for both pathological stage I and II lesions in a multivariate analysis [2]. Our results seem to indicate that the presence of teratoma does not only reflect a lower percentage of the most malignant element, namely EC, but it also signals differentiation towards more benign behaviour *per se*, since the prognostic value of teratoma was independent of the percentage of EC. Unlike previous studies, we distinguished between mature and immature teratoma and found that only the purported less aggressive mature subtype was associated with a low risk of relapse in multivariate analysis. Interestingly, it has been suggested that pure mature teratoma is more likely to be limited to the testis than its immature counterpart [23]. However, the presence of mature teratoma in the primary was recognised as a risk factor for developing a subsequent 'growing teratoma syndrome' [24].

Although clearly useful, knowledge of prognostic factors is not sufficient for clinicians who wish to make the right risk-based decisions. Therefore, a reproducible and simple prognostic factor-based classification separating patients into good and poor prognostic groups is required for routine clinical practice and to facilitate collaborative trials. A few studies have attempted to establish such a prognostic index [4,6,7,10]. Heidenreich and colleagues recently proposed a predictive index based on the percentage of EC and the presence of VI [10]. However, RFS was not evaluated in that study. Sogani and colleagues [7] identified a group of patients with the presence of VI and predominant EC histology among patients undergoing surveillance who had a very high risk of relapse (71%). However, this group was very small (only 7% of the entire cohort). These authors did not identify a low-risk group. In contrast, with our model, approximately a third of the patients were classified in the very low-risk group (no relapse among 27 patients) and slightly less than a third in the high-risk group (61% of relapses), while the remaining patients had an intermediate risk of relapse. To our knowledge, this is the first study to have identified a group of patients who did not relapse at all. Furthermore, the presence of mature teratoma in the testis tumour, the second determinant parameter in our prognostic index, is probably easier to evaluate than the percentage of EC. In our opinion, this simple prognostic index could be useful to clinicians pending validation on an independent series of patients since this investigation was retrospective.

In our opinions, surveillance alone may be recommended for patients in the low-risk group. Given the very low risk of relapse, a simplified surveillance protocol should be prospectively assessed in this subgroup of patients. For example, a CT scan of the abdomen, the pelvis and the thorax may be performed only twice a year during the first year, than once a year during 2 years. Tumour markers may be checked every 4 months the first year, then every 6 months the second year. A clinical surveillance should be prolonged after the 2 first years because late relapses, albeit rare, have been reported to occur after 2 years [4], as well as controlateral testis cancer [25]. In high-risk patients, RPLND does not appear to be a fully satisfactory strategy because the risk of recurrence after RPLND was high for both pathological stage I and II disease in the event of VI [2,16] or no teratoma [2] in the primary tumour. In this subset of patients, adjuvant chemotherapy could be an alternative strategy. In the Medical Research Concil (MRC) study, only one relapse was observed among 113 high-risk stage I patients treated

with two cycles of the BEP regimen [3]. Two cycles of BEP appear to be well tolerated, without clinically significant pulmonary toxicity and a very low risk of secondary leukaemia [3,26]. However, several questions are still pending concerning adjuvant chemotherapy in high-risk clinical stage I NSGCT [27]. A significant proportion of patients will be overtreated since there is no prognostic index identifying a subgroup of patients with a risk of relapse $>70\%$. Moreover, prognosis and treatment of relapses occurring after two cycles of adjuvant BEP remain to be defined.

In conclusion, our prognostic index identified a subgroup of patients with a very low risk of relapse that represents approximately one third of patients with stage I disease. The creation of an international collaborative group is urgently needed so that a consensus can be reached about the classification of stage I NSGCT, as was the case for advanced disease.

Acknowledgement

We thank Ms Lorna Saint Ange for editing the manuscript.

References

1. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. *N Engl J Med* 1998, **337**, 242–253.
2. 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.
3. 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.
4. 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**, 294–298.
5. Droz JP, van Oosterom AT. Treatment options in clinical stage I non-seminomatous germ cell tumours of the testis: a wager on the future? A review. *Eur J Cancer* 1993, **29A**, 1038–1044.
6. Read G, Stenning SP, Cullen MH, *et al*. Medical research council prospective study of surveillance for stage I testicular teratoma. *J Clin Oncol* 1992, **10**, 1762–1768.
7. Sogani PC, Perrotti M, Herr HW, *et al*. Clinical stage I testis cancer: long-term outcome of patients on surveillance. *J Urol* 1998, **159**, 855–858.
8. Young BJ, Bultz BD, Russel JA. Compliance with follow-up of patients treated for non-seminomatous testicular cancer. *Br J Cancer* 1991, **64**, 606–608.
9. Heidenreich A, Sesterhenn IA, Moul JW. Prognostic risk factors in low stage testicular germ cell tumours. *Cancer* 1997, **79**, 1641–1645.
10. Heidenreich A, Sesterhenn IA, Mostofi FK, Moul JW. Prognostic risk factors that identify patients with clinical stage I non-seminomatous germ cell tumours at low risk and high risk for metastasis. *Cancer* 1998, **83**, 1002–1011.
11. The International Germ Cell Cancer Collaborative Group. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol* 1997, **15**, 594–603.
12. Culine S, Kerbrat P, Bouzy J, *et al*. Are 3 cycles of bleomycin, etoposide and cisplatin or 4 cycles of etoposide and cisplatin equivalent regimens for patients with good-risk metastatic non seminomatous germ cell tumors? Preliminary results of a randomized trial. *Proc Am Soc Clin Oncol* 1999, **18**, 309a.
13. Gels ME, Hoekstra HJ, Sleijfer DT, *et al*. Detection of recurrence in patients with clinical stage I nonseminomatous testicular germ cell tumors and consequences for further follow-up: a single-center 10-year experience. *J Clin Oncol* 1995, **13**, 1188–1194.
14. Moul JW, McCarthy WF, Fernandez EB, Sesterhenn IA. Percentage of embryonal carcinoma and of vascular invasion predicts pathological stage in clinical stage I nonseminomatous testicular cancer. *Cancer Res* 1994, **54**, 362–364.
15. Sturgeon JFG, Jewett MAS, Alison RE, *et al*. Surveillance after orchidectomy for patients with clinical stage I nonseminomatous testis tumors. *J Clin Oncol* 1992, **10**, 564–568.
16. 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.
17. Albers P, Bierhoff E, Neu D, *et al*. Mib-1 immunohistochemistry in clinical stage I nonseminomatous testicular germ cell tumors predicts patients at low risk for metastasis. *Cancer* 1997, **79**, 1710–1716.
18. Sweeney CJ, Hermans BP, Heilman DK, *et al*. Results and outcome of retroperitoneal ymph node dissection for clinical stage I embryonal carcinoma-predominant testis cancer. *J Clin Oncol* 2000, **18**, 358–362.
19. Moul JW, Heidenreich A. Prognostic factors in low stage non-seminomatous testicular cancer. *Oncology* 1996, **10**, 1359–1376.
20. Pont J, Holtl W, Kosak D, *et al*. Risk-adapted treatment choice in stage I nonseminomatous testicular germ cell cancer by regarding vascular invasion in the primary tumor: a prospective trial. *J Clin Oncol* 1990, **8**, 16–20.
21. Fung CY, Kalish LA, Brodsky GL, *et al*. Stage I non-seminomatous germ cell testicular tumor: prediction of metastatic potential by primary histopathology. *J Clin Oncol* 1988, **6**, 1467–1473.
22. Sogani PC, Whitmore WF, Herr HW, *et al*. Orchidectomy alone in the treatment of clinical stage I nonseminoamtous germ cell tumor of the testis. *J Clin Oncol* 1984, **4**, 267–270.
23. Leibovitch I, Foster RS, Ulbright TM, Donohue JP. Adult primary pure teratoma of the testis. *Cancer* 1995, **75**, 2244–2250.
24. André F, Fizazi K, Culine S, *et al*. The growing teratoma syndrome: results of therapy and long-term follow-up of a rare complication of non seminomatous germ-cell tumours. *Eur J Cancer* 2000, **36**, 1389–1394.
25. Coogan CL, Foster RS, Simmons GR, *et al*. Bilateral testicular tumours. *Cancer* 1998, **83**, 547–552.
26. Behnia M, Foster R, Einhorn LH, Donohue J, Nichols CR. Adjuvant bleomycin, etoposide and cisplatin in pathological stage II non-seminomatous testicular cancer: the Indiana University experience. *Eur J Cancer* 2000, **36**, 472–475.
27. Keizer HJ. Clinical stage I non-seminomatous: Europe versus USA. A draw. *Eur J Cancer* 2000, **36**, 440–442.