implications of serum level monitoring. *Eur J Clin Oncol* 1984, **20**, 47–53.
5. Pastan I, Gottesman M. Multiple-drug resistance in human cancer. *New Engl J Med* 1987, **316**, 1388–1393.
6. Rothenberg M, Ling V. Multidrug resistance: molecular biology and clinical relevance. *J Natl Cancer Inst* 1989, **81**, 7–10.
7. Fojo AT, Ueda K, Slamon DJ, *et al.* Expression of a multidrug-resistance gene in human tumors and tissues. *Proc Natl Acad Sci USA* 1987, **84**, 265–269.
8. Moolenaar AJ, Niewind JWM, Oei IT. Estimation of o,p-DDD in plasma by gas–liquid chromatography. *Clin Chim Acta* 1977, **76**, 213–218.
9. Scheper RJ, Bulte JWM, Brakkee JGP, *et al.* Monoclonal antibody JSB-1 detects a highly conserved epitope of the P-glycoprotein associated with multidrug-resistance. *Int J Cancer* 1988, **42**, 389–394.
10. de Bruijn HWA, van Beeck Calkoen-Carpay T, Jager S, *et al.* The tumor marker CA125 is the common constituent of normal cervical mucus. *Am J Obstet Gynecol* 1986, **154**, 1088–1091.
11. van Slooten H, Schaberg A, Smeenk D, Moolenaar AJ. Morphologic characteristics of benign and malignant adrenocortical tumors. *Cancer* 1985, **55**, 766–773.
12. Bates SE, Shieh CY, Mickley CA, *et al.* Mitotane enhances cytotoxicity of chemotherapy in cell lines expressing a multipledrug resistance gene (mdr-1/P-glycoprotein) which is also expressed by adrenocortical carcinomas. *J Clin Endocrinol Metab* 1991, **73**, 18–29.
13. Touitou Y, Moolenaar AJ, Bogdan A, *et al.* O,p-DDD (mitotane) treatment for Cushing's syndrome: adrenal drug concentrations and inhibition *in vitro* of steroid synthesis. *Eur J Clin Pharmacol* 1985, **29**, 483–487.
14. Bricaire H, Luton JP. Douze ans de traitement médical de la maladie de Cushing. *Nouv Presse méd* 1976, **5**, 325–329.

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Feature Articles

Treatment Options in Clinical Stage I Non-seminomatous Germ Cell Tumours of the Testis: A Wager on the Future? A Review

J.P. Droz and A.T. van Oosterom

INTRODUCTION

THE PROGNOSIS of metastatic germ cell tumours of the testis has dramatically improved with the introduction of cisplatin-based chemotherapy [1]. One of the most important refinements in the treatment of these tumours is the use of prognostic factors to indicate risk-adapted treatments. This is currently used in the treatment of advanced disease [1]. It is noteworthy that even in the past the cure rate of patients with tumours localised in the testis only (clinical stage 1) was high [2, 3]. The standard treatment of these patients was either retroperitoneal lymph node dissection (RPLND) or radiotherapy to the retroperitoneal region and cure rates as high as 80–90% have been reported [2]. However, the "wait and see" policy (surveillance) emerged in the early 1980s [4] when it was proven that low volume metastatic disease could be cured by chemotherapy in the majority of cases and more reliable investigations including chest and abdominal computed tomography (CT) scan, but especially serum alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) measurements made earlier detection possible. This policy then became popular. Unfortunately, no evaluation of both modalities has been undertaken in a randomised trial. We review here the status of the different treatment options in localised testis cancer.

We only consider in this review non-seminomatous germ cell tumours of the testis as defined both in the World Health Organization (WHO) classification [5] and the English classification [6]. Clinical stage I disease is defined according to the Union Internationale Contre le Cancer staging system [7] as a disease without visceral and retroperitoneal lymph node metastases after physical examination, imaging and biochemical tests.

CLINICAL AND PATHOLOGICAL STAGE I, CLARIFYING THE PROBLEM

Clinical staging is based on clinical examination, measurement of serum tumour markers (AFP, HCG), chest radiographs and CT scan of the chest and abdomen with and without bilateral pedal lymphangiography. In clinical stage I disease there is no evidence of tumour spread demonstrated by these investigations. When postorchiectomy tumour marker levels remain elevated involvement of retroperitoneal lymph nodes or metastatic spread elsewhere is found in all cases [8]. One way to evaluate clinical staging is to compare the results of investigations with the results of surgical staging (that is RPLND). Table 1 summarises findings from different studies [9–23]. Three conclusions can be drawn from this table: (i) the false negative and false positive rates of lymphangiography and abdominal CT scan are approximately equal to 30 and 15%, respectively. (ii) From the data in the

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Table 1. Comparison of the results of the imaging techniques and the histopathological findings at retroperitoneal lymph node dissection (RPLND)

	Lymphangiography		CT scan		Lymphangiography + CT scan	
	Negative	Positive	Negative	Positive	Negative	Positive
Retrospective studies	187	165	97	129	595	59
[9–17, 19–23]	(134)	(24)	(57)	(18)	(463)	(17)
False negative	28%		41%		22.3%	
False positive		14%		13%		19%
McLeod *et al.* [18]	139	29	305	79	352	107
	(105)	(10)	(211)	(13)	(239)	(25)
False negative	32%		31%		32%	
False positive		34%		16%		23%

Number of patients with normal lymph nodes at RPLND in parentheses.

literature it is not clear how much lymphangiography adds to the CT scan. Data of the ongoing EORTC study must be awaited. (iii) The percentage of patients with clinical stage I disease who were actually pathological stage II disease at RPLND is 20 to 30% in all surgical series. It is noteworthy that no study reports the size of retroperitoneal lymph nodes found at the RPLND in clinical stage 1 patients with retroperitoneal involvement [9–23].

THE RESULT OF LUMBO-AORTIC RADIOTHERAPY: WHAT IS THE LESSON?

Tyrrel *et al.* [25] reported 88 patients treated by radiotherapy of whom 16 relapsed: 10 with visceral metastases, 6 in the retroperitoneum (but 2 of them did not actually receive the radiotherapy). Two factors which showed a significant correlation with relapse were identified: local extent of the primary tumour and postorchiectomy serum tumour marker levels [26]. Fossa *et al.* [27] reported 132 patients treated by radiotherapy; 33 of whom recurred (25%). In a series of 62 clinical stage I patients, van der Werf-Messing *et al.* [28] reported a 27% relapse rate which was higher in patients with vascular invasion (44%) than in patients free of vascular invasion (22%). Recently, Rorth *et al.* [29] reported 73 patients in a randomised trial who were treated by radiotherapy, 11 of whom had visceral metastases and none had solitary retroperitoneal relapse. The conclusion of these studies is that lumbo-aortic irradiation controls retroperitoneal metastases but, as could be expected of a locoregional treatment, fails to prevent the development of visceral metastases (the percentage being 15%).

RETROPERITONEAL LYMPH NODE DISSECTION: THE WAY OF TRUTH?

The first section of this review shows that RPLND allows determination of the actual stage of the disease. There are two groups of patients: those with stage II disease who are cured by RPLND and adjuvant chemotherapy [30] and those with stage I disease. The relapse rate in pathological stage I disease is 12% as is shown in Table 2. Of these relapses, one sixth (2% of all relapses) occurs in the retroperitoneum and the remainder in other sites. It is concluded that RPLND nearly completely excludes the risk of lumbo-aortic recurrence. For example, McLeod *et al.* [18] have reported only 4 patients with retroperitoneal recurrence without elevation of tumour marker levels. The consequence is that follow-up is easier and can be performed with tumour marker level measurement and routine chest X-ray.

Studies of prognostic factors were performed in two ways. The first type of prognostic study was designed to determine which clinical stage I patients were likely to be actual pathological stage II patients. Four studies have addressed this question [21–24] in either univariate [21] or multivariate analysis [22, 23, 24]. Javadpour *et al.* found three prognostic factors: presence of embryonal carcinoma, vascular invasion and extension to the spermatic cord [21]. Klepp *et al.* identified the following prognostic factors [22]: vascular invasion, normal pre-orchiectomy AFP level (when AFP level was not measured: absence of teratoma elements, absence of yolk sac elements). Fung *et al.* [23] in another multivariate analysis described three factors: pT $\geq$ 2, vascular invasion and less than 50% teratoma element. McLeod *et al.* [18] have shown that 60 of 459 patients (13%) have vascular invasion: two-thirds of them were pathological stage II patients, concluding that vascular invasion is highly predictive of retroperitoneal involvement. Sesterhenn *et al.* [24] found that patients with both vascular and lymphatic invasion were likely to be actually pathological stage II patients.

The second type of prognostic factor study was undertaken to define which pathological stage I patients were likely to recur [22, 24, 25]. Klepp *et al.* [22] found two factors: vascular invasion and absence of teratoma elements. Bredael *et al.* did not demonstrate strong prognostic factors: pT $\geq$ 2, presence of embryonal carcinoma [35]. Sesterhenn *et al.* [24] demonstrated that in pathological stage I disease, the relapse rate was 19.4% (12 of 62 cases) for those with venous/lymphatic invasion vs. 6% (10 of 168 cases) for those without invasion. In conclusion, vascular invasion seems to be the best prognostic factor of pathological stage II disease and recurrence.

The main adverse effect of RPLND is the loss of ejaculatory function, the incidence of which is strongly linked to the surgical technique. The loss of ejaculatory function is 100% with traditional bilateral suprahilar RPLND [2], 90% with modified infrahilar bilateral RPLND [36], 40% with modified unilateral RPLND [37] and less than 10% with nerve-sparing modified RPLND [19]. Three major arguments advocate the use of RPLND in clinical stage I disease: (i) an immediate knowledge of the actual stage of the patient, (ii) an easier follow-up procedure for pathological stage I patients, (iii) a low morbidity when nerve-sparing procedure is used. However, its use outside clinical studies cannot yet be advocated because it it not yet

Table 2. Review of the retroperitoneal lymph node dissection (RPLND) results in pathological stage I disease series

Author	No. of patients	No. of local* relapses	No. of distant† metastases	Total no. of recurrences	Survival (years)
Maier *et al.* [31] 1940–1965	109	?	?	29	73% (5)
Skinner and Leadbetter [2]	31	2	1	3	90% (5)
Staubitz *et al.* [32]	45	0	3	3	86% (5)
Clements *et al.* [33]‡ = Maier and Mittemeyer [34] 1968–1973	47	?	?	5	89% (3)
Bredael *et al.* [35]	138	3	9	12	96% (3)
Javadpour *et al.* [21]	54	0	4	4	100% (?)
Pizzocaro *et al.* [20]	55	0	8	8	96% (3)
Fung *et al.* [23]	55	4	7	11	100% (?)
Klepp *et al.* [22]	204	5	25	30	98% (6)
McLeod *et al.* [18]	264	4	23	27	97% (?)
Donohue *et al.* [19]	61	0	4	4	100% (?)
Total	1063	18 (1.7%)	84 (8.3%)	131 (12%)	

*Isolated retroperitoneal recurrence.
†May be additive with *.
‡Part of a randomised trial (RPLND + radiotherapy).

proven that the only 2% relapse rate of Table 2 also holds for this modified technique.

SURVEILLANCE PROCEDURE: THE WAY OF PROCRASTINATION?

In the late 1970s three facts changed the treatment policy in clinical stage I patients: (i) imaging procedures were more accurate, (ii) the observation of the results of lumbo-aortic radiotherapy and RPLND led to the conclusion that an involvement of lumbo-aortic lymph nodes was present in 20–25% of cases and that the incidence of visceral metastases was 10–15%, (iii) chemotherapy cured virtually all patients with low volume metastatic disease. Then in 1979 investigators at the Royal Marsden Hospital began a surveillance protocol in clinical stage I disease the results of which were first shown in 1982 [3]. After this, many studies were undertaken. Table 3 shows a summary of the most important published series of surveillance [29, 38–47].

Some important conclusions are available from these studies.
—The mean relapse rate is 30% (95% confidence interval: 26–33%) with a minimal follow-up of over 3 years.
—The characteristics of relapses are: a median delay of 5 months, 10% of them occurring more than 2 years after orchiectomy; elevated tumour marker level in two-thirds of the cases, this elevation being the only sign of recurrence in one-fifth of the cases; the site of recurrence only in the retroperitoneum in one half of the patients, half of them without any elevation of the tumour marker level.
—When the treatment of relapse is appropriate chemotherapy, the NED rate is 97%.
—The main prognostic factors of relapse are: presence of embryonal carcinoma (five out of seven studies), lymphatic invasion (three out of three studies), vascular invasion, absence of yolk sac tumour and pT $\geq$ 2 stage (two out of five studies).

The most important retrospective study was performed by the Medical Research Council [40] in 259 patients. A multivariate analysis of factors for recurrence showed that four factors retained significant prognostic value: vascular invasion, lymphatic invasion, absence of yolk sac tumour and presence of embryonal carcinoma. A simplified index scoring system was defined: patients with no or one poor risk factor were considered at low risk of relapse, patients with three or four poor risk factors were considered at high risk of relapse and the remaining patients with two poor risk factors have an intermediate risk of relapse. Table 4 shows the groups of patients and their expected relapse rate. It also shows the validation of this system in an independent population of patients treated between 1984 and 1987 whose evolution was recently reported [49].

In this population of 373 eligible patients there were 99 relapses (28%) which occurred after a median delay of 6 months [9 patients (10%) recurred after 24+ months]. 29 patients (30%) had an isolated elevation of tumour marker level and 61 had a retroperitoneal relapse. Advanced disease relapse was observed in 14 patients (15%) (8 stages IIC, 4 stages L2, 1 liver and 1 brain metastases [49]. It is concluded that patients of low and intermediate risk group have less than 25% risk of relapse and patients of the high risk group have a 50% risk of relapse. This latter group of patients represents a quarter of the whole population of patients with clinical stage I disease.

One interesting remark concerning the follow-up policy is that the relapse rate, the median time to relapse and the stage of relapse is not influenced by the frequency of CT scanning when the clinical examination, chest X-ray and tumour marker level measurements are performed at least every 2 months [40]. However, the policy to perform an abdominal CT scan may be every 2 to 3 months [50].

Some authors have pointed out the difficulty of assessing lymphatic and vascular invasion. A strict definition of vascular invasion is needed [51–53]. It is (i) the penetration of tumour cells with or without a thrombosis within the lumen of the vessel, (ii) the destruction of the endothelium and the adhesion of endoluminal tumour cells to the endothelium. Freedman *et al.* reported the following incidences of the poor risk factors [40]: lymphatic invasion (19%), vascular invasion (50%), absence of yolk sac (31%), presence of embryonal carcinoma (87%). Patients who have only two of the four risk factors have a 15% relapse rate. Thus, if one considers only the 50% patients with vascular invasion, their relapse rate is 43%. This observation explains the fact that some investigators have only considered this prognostic factor [54].

Table 3. Surveillance studies—prognostic factors studies

Reference	38	39	40	42	43	44	45	29	47	Total
No. of patients	45	71	259	36	46	100	24	76	105	762
No. of relapses (%)	9 (20%)	21 (29%)	70 (27%)	12 (33%)	21 (29%)	31 (31%)	6 (25%)	23 (30%)	37 (35%)	220 (29%)
mk(+)	5	14	?	7	4	26	?	16	19	67%
mk(+) only	1	1	17	1	1	8	2	2	6	18%
LAln only	7	8	27	4	2	9	2	14	25	45%
LAln only with mk(−)	3	2?	26	1	0	?	?	4	6	24%
Other sites ± LAln	2	12	31	6	10	14	1	7	3	45%
Median delay (months)	4	6	6	6	4	4	4	4	6.3	5
No. of patients with delay >2 years	1	1	5	2	2	1	2	4	0	8%
No. of NED patients	44	69	256	35	44	97	24	76	104	739 (97%)
PF analysis	Univariate	Univariate	Multivariate	Univariate	Univariate	Multivariate Dunphy [45]	ND	Multivariate Jacobsen [48]	Univariate	
Vascular invasion	ND	−	+	−	ND	6		+	+	3/6
Lymphatic invasion	ND	ND	+	+	ND	+		ND	ND	3/3
Yolk sac tumour	ND	ND	Absence +	−	−	−		Absence +	ND	2/5
Presence of embryonal carcinoma	+	+	+	−	−	+		+	+	6/8
pT ≥ 2	ND	+	−	−	+	ND		6	ND	2/5
High AFP level	ND	ND	−	−	ND	ND		−	ND	0/3

PF: prognostic factors; mk: tumour marker level; pT ≥ 2: UICC classification (3); LAln: lumbo-aortic lymph nodes; AFP: alpha-fetoprotein; NED: non-evolutive disease; ND: not done.

CHEMOTHERAPY IN HIGH-RISK RELAPSE PATIENTS: THE WAY OF THE FUTURE?

The outstanding results of chemotherapy in low volume metastatic disease [1] and as adjuvant treatment in postsurgical stage II disease [30] led some investigators to study adjuvant chemotherapy after orchiectomy in high-risk clinical stage I patients. Only three studies have been reported in the modern chemotherapy era. Pont *et al.* [54] reported the results of a study of 22 patients without vascular invasion treated by surveillance only and of 18 patients with vascular invasion treated by two cycles of adjuvant bleomycin, etoposide, cisplatin (BEP) chemotherapy. There were one and two relapses in the surveillance and chemotherapy groups, respectively, after a median follow-up time of 30 months (3–50 months). One of the chemotherapy group patients recurred in the retroperitoneum and only mature teratoma was found at RPLND. Gimmi *et al.* [55] treated 28 patients with embryonal carcinoma and/or pT ≥ 2 stage by orchiectomy and two cycles of a modified BEP chemotherapy regimen. No relapse and only one growing mature teratoma were observed after a median follow-up of 30 months (range 7–74 months).

Table 4. The Medical Research Scoring System for relapse [39]: *validation of the model* [49]

	Study population [40]		Independant population [49]	
Risk group	No. of patients (% total)	No. of relapses (%)	No. of patients (% total)	No. of relapses (%)
Low risk	89 (38)	8 (9)	141 (38)	24 (17)
Intermediate risk	89 (38)	21 (24)	142 (38)	33 (23)
High risk	55 (24)	32 (58)	83 (24)	39 (47)
Total	233	61 (26)	366	96 (26)

Low risk group: 0 or one adverse prognostic factors; Intermediate risk group: two adverse prognostic factors; High-risk group: three or four adverse prognostic factors.

A prospective phase II trial of chemotherapy in patients with three to four poor risk factors is currently under evaluation by the Medical Research Council [56]. 61 patients received two courses of cisplatin 100 mg/m^2, etoposide 120 mg/m^2 day for 3 days and bleomycin 30 mg weekly for 3 weeks. With a median follow-up of 14 months (0–41 months), 57 patients have completed the two cycles of chemotherapy, 32 have been followed for at least 12 months. No relapse has yet been observed at the time of the first report [56]. Another study was reported by Madej and Pawinski [57]. 30 patients with either vascular invasion, lymphatic invasion or involvement of the epididymis or rete testis were treated by two cycles of platinum, vinblastine and bleomycine combination chemotherapy after orchiectomy. None of them relapsed after a follow-up of 12–60 months.

TRIALS IN CLINICAL STAGE I DISEASE: THE WAY OF WISDOM?

The aim of a trial in clinical stage I disease is to decrease the aggressiveness and morbidity of the treatment and to maintain the cure rate eventually observed. One question is the impact of possible relapses when this event is considered as acceptable if it is easily cured by salvage chemotherapy. Thus, such a trial must consider not only the end-result (cure which must approach 100%) but also the morbidity and the cost of the treatment, and an evaluation of the quality of life.

Some preliminary observations can be made:

—The surgical procedure must be a nerve-sparing unilateral retroperitoneal lymph node dissection as it insures a less than

10% loss of ejaculation function [19]. It is questionable whether this operation can be performed by urologists who are not particularly skilled in the treatment of testicular cancer.

—The number of cycles of postorchiectomy adjuvant chemotherapy regimen is difficult to assess.

On the one hand one could consider that the first course of chemotherapy given to patients with advanced disease can induce more than a 50% decrease in tumour volume and that the half-life of tumour marker levels is constant during the different courses of chemotherapy [58]. Thus only one course of chemotherapy could be administered.

On the other hand it has been demonstrated that the optimal treatment of low volume metastatic disease is three cycles of BEP [59]. However, any decrease of the chemotherapy is detrimental: the omission of bleomycin in a protocol with three courses of BEP induces a high incidence of failure [60]. It has been demonstrated that two courses of cisplatin-containing chemotherapy avoid the risk of relapse in pathological stage II disease [30]. It implies that two courses of chemotherapy are sufficient to control microscopic disease. Conversely, it can be advocated to deliver three courses of BEP, as the volume of retroperitoneal disease is unknown.

—When a relapse occurs after the surveillance policy or the RPLND, the optimal chemotherapy is three courses of BEP to patients with low volume metastatic disease (80% of patients) [1, 59, 60] and four courses of BEP to patients with advanced disease (20% of patients) [1, 60].

—When a relapse occurs after adjuvant chemotherapy, the salvage chemotherapy would be four courses of cisplatin, ifosfamide and either vinblastine or etoposide [62] if the treatment indications in the salvage setting are transposed in this situation. However, the long-term NED rate is generally not more than 20–30% after salvage chemotherapy [62].

—The follow-up procedure in a surveillance policy can be the following: clinical examination, chest X-ray, abdominal CT scan and tumour marker level measurements should be carried out every 2 months during the first 2 years then every 3 months afterwards.

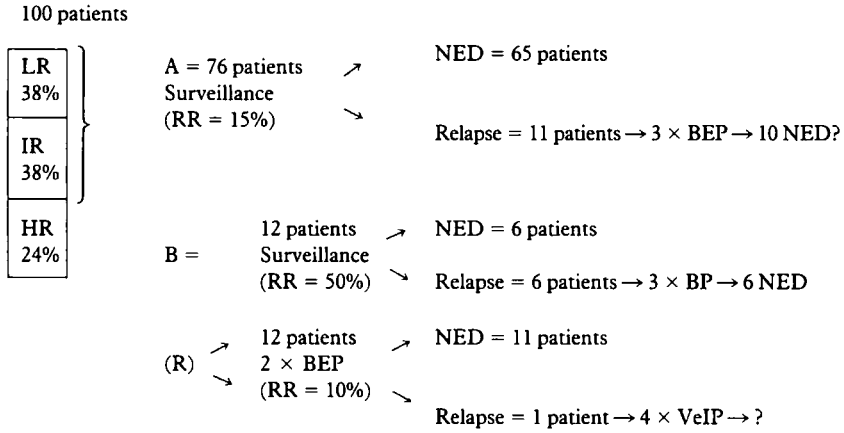
—The quality of life and morbidity evaluation must consider the psychological stress of living with the knowledge that there is a possibility of relapse in the surveillance policy, the loss of ejaculatory function and post-operative problems after the RPNLD, the different toxicities and the psychological impact of the chemotherapy in either the surveillance policy or the chemotherapeutic approach.

Several trial designs in clinical stage I disease can be conceived. The selection of high-risk for relapse patients could use either the Medical Research Council scoring system or simply vascular invasion. We have chosen to use the Medical Research Council criteria in the following hypothesis. Tables 5 and 6 show two trial hypotheses. They summarise the number of patients treated by chemotherapy (with the number of courses) and the number of patients submitted to RPLND.

—In the first design (Table 5) patients with low and intermediate risk are followed and high-risk patients are randomised to either surveillance (and chemotherapy in the event of a relapse) or adjuvant postorchiectomy chemotherapy. This trial is the randomised form of the phase II trial which is currently under evaluation by the Medical Research Council.

—In the second design (Table 6) patients with low and intermediate risk of relapse are followed and patients with high risk of relapse are randomised to either RPLND or adjuvant postorchiectomy chemotherapy. This trial studies the relative weight of either performing a RPLND in all patients or treating twice fewer patients by chemotherapy.

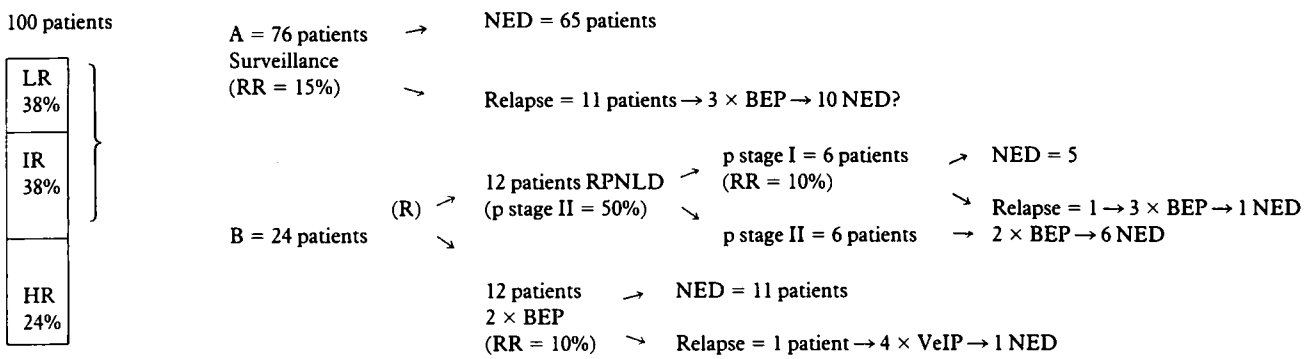
Table 5. Design of a trial which study the role of delayed treatment of relapse vs. adjuvant postorchiectomy chemotherapy (CT) in high-risk (HR) patients



	No. of patients treated by CT	No. of courses of BEP
A	11	33
B (surv)	6	18
B (CT)	12	24

(R) = randomisation; LR = low risk; NED = non-evolutive disease; IR = intermediate risk; BEP = bleomycin, etoposide, cisplatin; RR = risk of relapse; VeIP = vinblastine, ifosfamide, cisplatin; CT = chemotherapy.

Table 6. Design of a trial comparing retroperitoneal lymph node dissection (RPLND) and adjuvant postorchiectomy chemotherapy (CT) in high-risk (HR) patients



	No. pts treated by CT	No. of courses of BEP	No. of RPNLD
A =	11 7	33	0
B (RPLND)	12	15	12
B (CT)		24	0

(R) = randomisation NED = non-evolutive disease; LR = low risk; p stage (III) = pathological stage I (II); BEP = bleomycin, etoposide, cisplatin; RR = risk of relapse; VeIP = vinblastine, ifosfamide, cisplatin; CT = chemotherapy.

CONCLUSION

Our knowledge on clinical stage I disease has greatly improved during the 1980s. We have better insight in the prognostic factors, the side-effects of retroperitoneal lymph node dissection and the relapse treatment. However, further information on the exact relationships between prognostic factors is needed. In particular, the identification of one strong prognostic factor is preferred over a score of different factors. This prognostic factor must be easily assessed, and be a good predictor of relapse. Regarding the design of the trials we must consider two realities: (i) there are two different attitudes in the international practice (RPLND and surveillance policy) which must be taken in account (design of a pragmatic trial); (ii) the role of adjuvant postorchiectomy chemotherapy must be assessed (design of an explanatory trial).

On these bases the study of the treatment of clinical stage I non-seminomatous germ cell tumours need large scale trials which require an international cooperation, where we favour a study as shown in Table 4.

1. Einhorn LH. Testicular cancer: a new and improved model. *J Clin Oncol 1990*, **8**, 1777–1781.
2. Skinner DG, Leadbetter WF. The surgical management of testis tumors. *J Urol* 1971, **106**, 84–93.
3. Peckham MJ, Barret A, McElwain TJ, Hendry WF. Combined management of malignant teratoma of the testis. *Lancet* 1979, ii, 267–270.
4. Peckham MJ, Barrett A, Husband JE, Hendry WF. Orchiectomy alone in treatment stage I non-seminomatous germ-cell tumours. *Lancet* 1982, ii, 678–680.
5. Mostofi FK, Sobin LH. International Histological Classification of Tumors of Testes (no. 16). Geneva, World Health Organization, 1977.
6. Pugh, RCB, Cameron KM. Teratoma. In Pugh RCB, ed. *Pathology of the Testes*. Oxford, Blackwell Scientific Publications, 1976, 199–244.
7. IUAC. TNM Classification of Malignant Tumours, Fourth edition. Berlin, Springer, 1987, 127–129.
8. Klepp O, Flodgren P, Maartman-Moe D, *et al.* Early clinical stages (CS1, CS1Mk + and CS2A) of non-seminomatous testis cancer. *Ann Oncol* 1990, **1**, 281–288.
9. Sidi AA, Lange PH, Fraley EE. Staging of testicular cancer. In Javadpour N, ed. *Principles and Management of Testicular Cancer*. New York, THEME Inc. 1986, 216–233.
10. Thomas JL, Bernardino ME, Bracken RB. Staging of testicular carcinoma: comparison of CT and lymphangiography. *Am J Radiol* 1981, **137**, 991–996.
11. Richie JP, Garnick MB, Finberg H. Computerized tomography: how accurate for abdominal staging of testis tumors? *J Urol* 1982, **127**, 715–717.
12. Dunnick NR, Javadpour N. Value of CT and lymphography: distinguishing retroperitoneal metastases from non-seminomatous testicular tumors. *Am J Radiol* 1981, **136**, 1093–1099.
13. Wobbes Th, Blom JMH, Oldhoff J, Schraffordt-Koops H. Lymphography in the diagnosis of non-seminoma tumours of the testis. *J Surg Oncol* 1982, **19**, 1–4.
14. Rowland RG, Weisman D, Williams SD, Einhorn LH, Klatte EC, Donohue, JP. Accuracy of preoperative staging in stages A and B non-seminomatous germ cell testis tumors. *J Urol* 1982, **127**, 718–720.
15. Lien HH, Kolbenstvedt A, Talle K, Fossa SD, Klepp O, Ous S. Comparison of computed tomography, lymphography and phlebography in 200 consecutive patients with regard to retroperitoneal metastases from testicular tumor. *Radiology* 1983, **146**, 129–132.
16. Tesoro-Tess JD, Pizzocaro G, Zanoni F, Musumeci R. Lymphangiography and computerized tomography in testicular carcinoma: how accurate in early stage disease? *J Urol* 1985, **133**, 967–970.
17. Ehrlichman RJ, Kaufman SL, Siegelman SS, Trump DL, Walsch PC. Computerized tomography and lymphangiography in staging testis tumors. *J Urol* 1981, **126**, 179–181.
18. McLeod DG, Weiss RB, Stablein DM, *et al.* Staging relationships and outcome in early stage testicular cancer: a report from the testicular cancer intergroup study. *J Urol* 1991, **145**, 1178–1183.
19. Donohue JP, Foster RS, Rowland RG, Bihrle R, Jones J, Geier G. Nerve-sparing retroperitoneal lymphadenectomy with preservation of ejaculation. *J Urol* 1990, **144**, 287–292.
20. Pizzocaro G, Salvioni R, Zanoni F. Unilateral lymphadenectomy in intra-operative stage I non-seminomatous germinal testis cancer. *J Urol* 1985, **134**, 485–489.
21. Javadpour N, Canning DA, O'Connel KJ, Young JD. Predictors of recurrent clinical stage I non-seminomatous testicular cancer. A prospective clinico-pathologic study. *Urology* 1986, **27**, 508–511.
22. Klepp O, Olsson Am, Henrikson H, *et al.* Prognostic factors in clinical stage I non-seminomatous germ cell tumors of the testis:

multivariate analysis of a prospective multicenter study. *J Clin Oncol* 1990, **8**, 509–518.
23. Fung C, Kalish LA, Brodsky GL, Richie JP, Garnick MB. Stage I non-seminomatous germ cell testicular tumor: prediction of metastatic potential by primary histopathology. *J Clin Oncol* 1988, **6**, 1467–1473.
24. 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.
25. Tyrrell CJ, Peckham MJ. The response of lymph node metastases of testicular teratoma to radiation therapy. *Br J Urol* 1976, **48**, 363–370.
26. Raghavan D, Peckham MJ, Heyderman E, Tobias JS, Austin DE. Prognostic factors in clinical stage I non-seminomatous germ-cell tumours of the testis. *Br J Cancer* 1982, **45**, 167–173.
27. Fossa SD, Stenwig AE, Lien HH, Ous S, Kaalhus O. Non-seminomatous testicular cancer clinical stage I: prediction of outcome by histopathological parameters. A multivariate analysis. *Oncology* 1989, **46**, 294–300.
28. Van Der Werf-Messing B, Auerbach WM, Van Putten WLJ. Non-seminoma testis treated by irradiation at the Rotterdamsch Radiotherapeutisch Institut: the risk of metastasis. *Radiother Oncol* 1984, **2**, 101–105.
29. Rorth M, Jacobsen GK, Von Der Maase H, *et al.* Surveillance alone versus radiotherapy after orchiectomy for clinical stage I non-seminomatous testicular cancer. *J Clin Oncol* 1991, **9**, 1543–1548.
30. Williams SD, Stablein DM, Einhorn LH, *et al.* Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. *N Engl J Med* 1987, **317**, 1483–1438.
31. Maier JG, Van Buskirk KE, Sulak MH, Perry RH, Schamber DT. An evaluation of lymphadenectomy in the treatment of malignant testicular germ cell neoplasms. *J Urol* 1969, **101**, 356–359.
32. Staubitz WJ, Early MS, Magoss IV, Murphy GP. Surgical management of testis tumor. *J Urol* 1974, **111**, 205–209.
33. Clements JC, McLeod DG, Weisbaum GS, Stutzman RE. Radiation therapy for non-seminomatous germ cell tumors of the testis: a reappraisal. *J Urol* 1981, **126**, 490–492.
34. Maier JG, Mittemeyer B. Carcinoma of the testis. *Cancer* 1977, **39**, 981–986.
35. Bredael J, Vugrin D, Whitmore WF. Recurrences in surgical stage I non-seminomatous germ cell tumors of the testis. *J Urol* 1983, **130**, 476–1478.
36. Narayan P, Lange PH, Fraley EE. Ejaculation and fertility after extended retroperitoneal lymph node dissection for testicular cancer. *J Urol* 1982, **127**, 685–688.
37. Fossa SD, Ous S, Abylholm T, *et al.* Post-treatment fertility in patients with testicular cancer. I. Influence of retroperitoneal lymph node dissection on ejaculation potency. *Br J Urol* 1985, **57**, 204–209.
38. Sogani PC, Whitmore WF, Herr HW, *et al.* Orchiectomy alone in the treatment of clinical stage I non-seminomatous germ cell tumor of the testis. *J Clin Oncol* 1984, **2**, 267–270.
39. Pizzocaro G, Zanoni F, Milani A, *et al.* Orchiectomy alone in clinical stage I non-seminomatous testis cancer: a critical appraisal. *J Clin Oncol* 1986, **4**, 35–40.
40. Freedman LS, Parkinson MC, Jones WG, *et al.* Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchiectomy alone. *Lancet* 1987, **i**, 294–298.
41. Hoskin P, Dilly S, Easton D, Horwich A, Hendry W, Peckham MJ. Prognostic factors in stage I non-seminomatous germ-cell testicular tumors managed by orchiectomy and surveillance: implications for adjuvant chemotherapy. *J Clin Oncol* 1986, **4**, 1031–1036.
42. Thompson PI, Nixon J, Harvey VJ. Disease relapse in patients with stage I non-seminomatous germ cell tumor of the testis on active surveillance. *J Clin Oncol* 1988, **6**, 1597–1603.
43. Raghavan D, Colls B, Levy J, *et al.* Surveillance for stage I non-seminomatous germ-cell tumours of the testis: the optimal protocol has not yet been defined. *Br J Urol* 1988, **61**, 522–526.
44. Swanson D, Johnson DE. M.D. Anderson experience with surveillance for clinical stage I disease. In Johnson DE, Logothetis CJ, Von Eschenbach AC, eds. *Systemic Therapy for Genitourinary Cancers*. Chicago, Year Book Medical Publishers, 1989, 304–311.
45. Dunphy, C, Ayala AG, Swanson DA, Ro JY, Logothetis C. Clinical stage I non-seminomatous and mixed germ cell tumors of the testis. A clinicopathologic study of 93 patients on a protocol after orchiectomy alone. *Cancer* 1988, **62**, 1202–1206.
46. Patel S, Richardson RL, Kvols L, Zincke H. Observation after orchiectomy in clinical stage I non-seminomatous germ cell tumor of testis. *Am J Clin Oncol* 1990, **13**, 379–381.
47. Sturgeon JFG, Jewett MAS, Alison RE, *et al.* Surveillance after orchiectomy for patients with clinical stage I non seminomatous testis tumors. *J Clin Oncol* 1992, **10**, 564–568.
48. Jacobsen GK, Rorth M, Osterlind K, *et al.* Histopathological features in stage I non-seminomatous testicular germ cell tumours correlated to relapse. *APMIS* 1990, **98**, 377–382.
49. 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.
50. Husband J. Advances in tumour imaging. In Horwich A, ed. *Testicular Cancer. Investigation and Management*. London, Chapman and Hall Medical, 1991, 15–31.
51. Moriyama N, Daly JJ, Keating MA, Lin C, Prout GR. Vascular invasion as a prognosticator of metastatic disease in non-seminomatous germ cell tumors of the testis. Importance in "surveillance only" protocols. *Cancer* 1985, **56**, 2492–2498.
52. Hoertl W, Kosak D, Pont J, *et al.* Testicular cancer: prognostic implication of vascular invasion. *J Urol* 1987, **137**, 683–685.
53. Rodriguez PN, Hafez GR, Messing EM. Non-seminomatous germ cell tumour of the testicle: does extensive staging of the primary tumour predict the likelihood of metastatic disease? *J Urol* 1986, **136**, 604–608.
54. Pont J, Hoertl W, Kasak, *et al.* Risk-adapted treatment choice in stage I non-seminomatous testicular germ cell cancer by regarding vascular invasion in the primary tumor: a prospective trial. *J Clin Oncol* 1990, **8**, 16–20.
55. Gimmi C, Sonntag R, Brunner K, Studer U. Adjuvant treatment of high risk clinical stage I testicular carcinoma with cisplatin, bleomycin and vinblastine or etoposide. *Proc Am Soc Clin Oncol* 1990, **9**, 140.
56. Cullen, M. Management of stage I non-seminoma: surveillance and chemotherapy. In Horwich A, ed. *Testicular Cancer; Investigation and Management*. London, Chapman and Hall Medical, 1991, 149–166.
57. Madej G, Pawinski A. Risk-related adjuvant chemotherapy for stage I non-seminoma of the testis. *Clin Oncol* 1991, **3**, 270–272.
58. Oliver RT, Dahlival HS, Hope-Stone HF, Blandy JP. Short-course etoposide, bleomycin and cisplatin in the treatment of metastatic germ cell tumours. Appraisal of its potential as adjuvant chemotherapy for stage I testis tumours. *Br J Urol* 1988, **61**, 53–58.
59. Einhorn LH, Williams SD, Loehrer PJ, *et al.* A comparison of four versus three courses of cisplatin, VP16 and bleomycin in favorable prognosis disseminated germ cell tumors. *J Clin Oncol* 1989, **7**, 387–391.
60. Loehrer PJ, Elson P, Johnson DH, Williams SD, Trump DL, Einhorn LH. A randomized trial of cisplatin plus etoposide with or without bleomycin in favourable prognosis disseminated germ cell tumors: an ECOG study. *Proc Am Soc Clin Oncol* 1991, **10**, 169.
61. Williams SD, Birch R, Einhorn LH, *et al.* Treatment of disseminated germ cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med* 1987, **316**, 1435–1440.
62. Loehrer PJ, Einhorn JL, Williams SD. VP16 plus ifosfamide plus cisplatin as salvage therapy in refractory germ cell cancer. *J Clin Oncol* 1986, **4**, 528–536.

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