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Original Paper

Risk-adapted Treatment of Clinical Stage 1 Non-seminoma Testis Cancer

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250 patients with clinical stage 1 non-seminomatous germ cell tumours of the testis (NSGCT 1) were included into a prospective multicentre protocol during 1990–1994 and treated according to three risk strata: patients without tumour cell invasion of vascular structures in the testis (VASC–) and elevated serum AFP levels (AFP+) at orchiectomy were considered low risk (LR) and only observed closely. VASC– and AFP– or VASC+ and AFP+ patients were presumed intermediate risk (IR) and pathologically staged (PS) by retroperitoneal lymph node dissection (RPLND). VASC+ and AFP– patients were regarded as high risk (HR) and received adjuvant chemotherapy (PEB × 3). At a median observation time of 40 (7–68) months, all patients were alive and without evidence of active germ cell cancer. The actuarial relapse rate in the 106 LR patients was 22%, and 70% (14/20) had elevated serum tumour markers at relapse. One of 32 (3%) HR patients relapsed with a resectable retroperitoneal mature teratoma despite adjuvant chemotherapy. Only 14% of the 99 IR patients who underwent RPLND had PS2 disease, and the actuarial relapse rate in 85 PS1 patients was 18%. This multicentre study demonstrated that excellent therapeutic outcome is possible when 18 comparatively small urological and oncological centres follow a strict and formal cancer care programme. The useful prognostic effect of VASC was once again verified. Pathological staging by RPLND in NSGCT1 is, in our opinion, not necessary, with presumed low-risk patients offered surveillance and high-risk patients offered adjuvant chemotherapy. © **1997 Elsevier Science Ltd.**

Key words: testicular cancer, stage 1, staging, risk-adapted, surveillance, retroperitoneal, adjuvant chemotherapy, serum tumour markers, patient load

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INTRODUCTION

DESPITE MODERN staging procedures with CT and monitoring of serum tumour markers, 20–40% of the patients with clinical stage I non-seminomatous testicular germ cell tumours (NSGCT1) have subclinical metastatic disease and will relapse if they are only observed and followed up after

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orchiectomy. Many risk factors for metastatic disease have been defined over the last two decades, but all investigators seem to agree that invasion of tumour cells into vascular structures in the testis is the most robust and useful prognostic factor [1–5]. In a prior SWENOTECA study [3] of 295 patients with NSGCT1 who all underwent pathological staging by retroperitoneal lymph node dissection (RPLND), we found that 38% had subclinical metastatic disease and would have relapsed if only observed closely. Tumour cell invasion into vascular structures in or near the primary testis tumour, a normal pre-orchiectomy serum AFP (alpha-feto protein) level (or absence of yolk sac tumour cells in the primary tumour), and a short period between orchiectomy and final staging of the patient have been associated with increased risk of metastatic disease or relapse [3]. An association between the presence of yolk sac elements in the primary tumour [1] or a pre-orchiectomy serum AFP elevation [9] and a seemingly paradoxical reduced risk of occult metastases in NSGTC1 has also been described. In our previous study [3] we found that NSGCT1 patients who had both the favourable risk factors no vascular invasion (VASC–) and elevated AFP serum levels (AFP+) had only a 20% risk of having subclinical metastases (the combined risk of either having PS2 disease at RPLND or of relapse if they were PS1). Clinical stage 1 patients with VASC– and AFP– had a 38% risk, those with VASC+ and AFP+ had 58% and those with both the unfavourable risk factors (VASC+ and AFP–) had a 77% risk of having subclinical metastases. Patients who had PS1 disease at staging RPLND had a 35% risk of relapse if they had VASC +, but only 10% of the PS1 patients with VASC– relapsed. Based upon these findings, we designed a risk-adapted treatment and follow-up programme for our NSGCT1 patients.

PATIENTS AND METHODS

250 consecutive patients with NSGCT1 were included by 13 Swedish and 5 Norwegian hospitals into this prospective multicentre study during 1990–1994 (Table 1). After inguinal orchiectomy, the patients were clinically staged by chest X-ray and chest, abdominal and pelvic CT and repeated serum tumour marker analysis over a 6-week period and with special emphasis on monitoring the serum tumour marker pattern. Only patients with normalisation of their tumour markers or a decline in marker levels according to expected values were included. If no metatastic disease was found, they were considered clinical stage 1 and treated according to three risk strata: patients without tumour cell invasion of vascular structures in the testis (VASC–) and with an elevated serum AFP levels (AFP+) at orchiectomy were considered low risk (LR) and only observed closely. Patients with VASC– and AFP– or with VASC+ and AFP+ were presumed intermediate risk (IR) and pathologically staged (PS) by a unilateral or nerve-sparing RPLND. If retroperitoneal metastases were revealed by RPLND (PS2 disease), they received three courses of adjuvant chemotherapy with standard PEB (cisplatin, etoposide and bleomycin) chemotherapy [6]. VASC+ and AFP– patients were regarded as high risk (HR) and received three courses of adjuvant chemotherapy with PEB. PS2 disease found at staging RPLND were considered as a relapse at the time of RPLND in the actuarial analyses of relapse rates, in order to compare the relapse rate and patterns of relapse between the different risk strata. All patients were followed according to a detailed follow-up programme after completion of the clinical staging and primary treatment. Relapsing patients received 3–4 courses of PEB chemotherapy and supplementary surgical resection of any residual disease after chemotherapy. The histopathological examination of the primary tumour was performed by the Departments of Pathology of the SWENOTECA hospitals treating individual NSGCT1 patients. All patient data forms were sent to the SWENOTECA secretariats in Sweden or Norway where they were verified and computerised using the MEDLOG data management package.

RESULTS

Survival and overall follow-up

3 patients were censored from follow-up due to emigration after 24, 40 and 51 months after orchiectomy, but none had relapsed at the time of emigration. Follow-up is complete for all the remaining 247 patients. Survival status for all these 247 patients were cross-checked against the National Bureaus of Statistics in the two countries and was complete as of September 1, 1995. The median observation time was 40 months (7–68) from the time of orchiectomy. None of the 250 patients are reported dead from any cause, so the crude survival is 100% (Figure 1). All the 49 patients with PS2 or relapse from clinical stage 1 were in first and sustained remission after chemotherapy at last follow-up.

Table 1. Inclusion of patients by the participating SWENOTECA hospitals (n = 250)

Sweden	*No. of patients*	*Norway*	*No. of patients (n = 111)*
Lund	29	Bergen	48
Gøteborg	22	Trondheim	33
Uppsala	17	Tromsø	14
Stockholm (Søders.h)	16	Ullevål (Oslo)	12
Linkøping	15	Aker (Oslo)	4
Umeå	12		
Malmø	9		
Jønkøping	6		
Karlstad	4		
Ørebro	4		
Skøvde	2		
Boden	2		
Sundsvall	1		

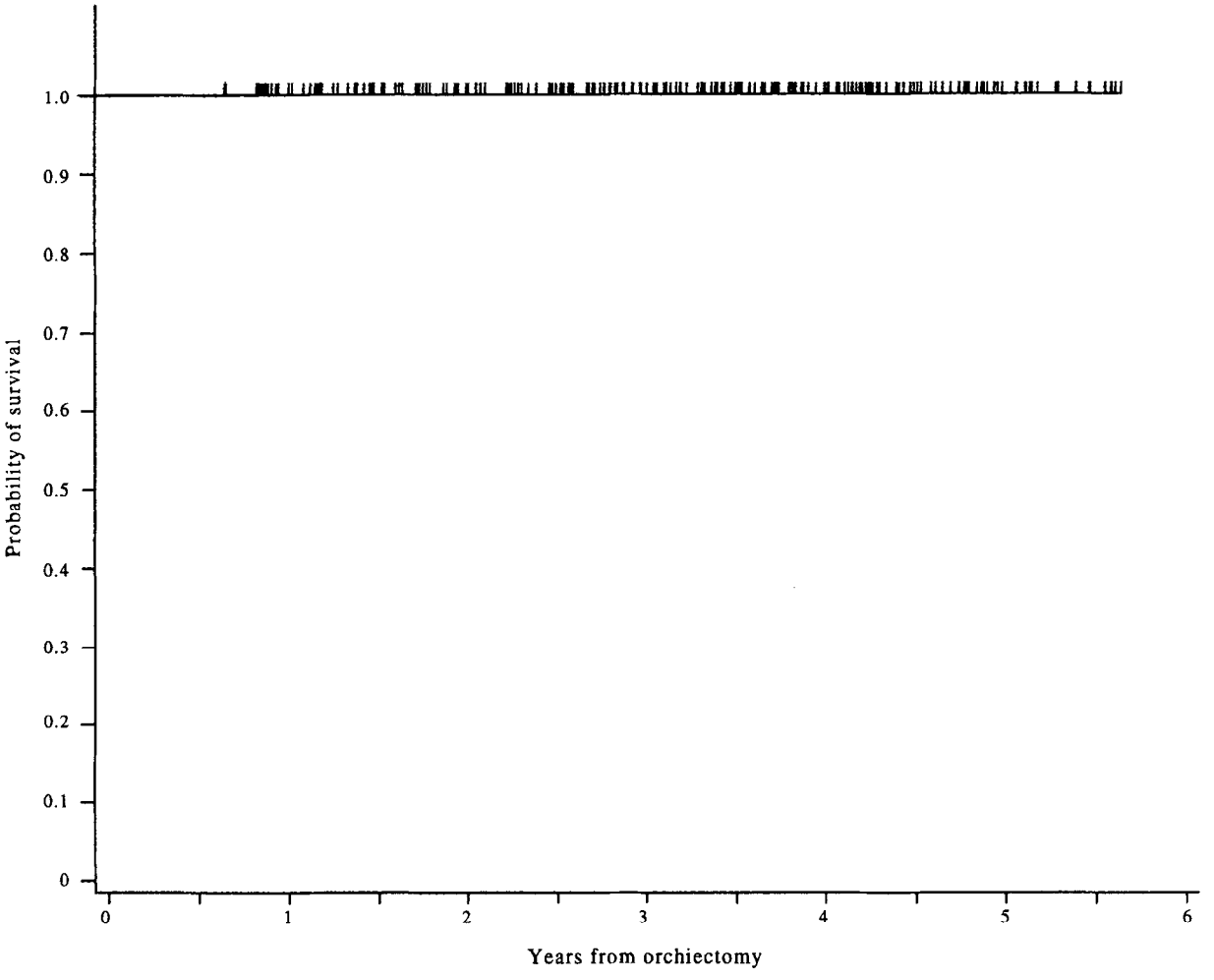

Figure 1. Crude survival of all the 250 patients included in the SWENOTECA II study (1990–1995). The median observation time from orchiectomy was 40 months (7–68).

Risk groups and metastases/relapse

Of the 250 patients, 106 (42.4%) were classified as having a low risk, 109 (43.6%) as intermediate risk and 34 (13.6%) with a presumed high risk of subclinical disease according to our prospective risk stratification. One patient could not be classified due to lack of pre-orchiectomy AFP measurement. 16 (6.4%) of the 250 patients did not receive treatment according to the protocol (Table 2), but we consider 11 of these to be evaluable for PS2 disease or relapse in relation to our postulated risk factors, and/or the effect of adjuvant chemotherapy in high-risk patients. PS2 disease was regarded as a relapse at the time of RPLND for those who underwent staging RPLND. The actuarial risk of relapse after orchiectomy for patients in the three risk groups is illustrated in Figure 2. The overall actuarial risk of relapse (including PS2 disease at staging RPLND) for all the 245 patients was 22%. The distribution of risk factors in the 245 evaluable patients is shown in Table 3.

Patterns of relapse

Low-risk patients. The actuarial relapse rate in the 106 evaluable low-risk patients was 22%. Median time to relapse was 6 months and only 2 patients relapsed later than 2 years from orchiectomy. 15 (75%) of the 20 low-risk patients under surveillance who relapsed, developed retroperitoneal metastases. The median diameter of

Table 2. Patients not treated according to the protocol

Situation	Treatment given	No. of patients
AFP unknown, VASC–	Surveillance	1*
Low risk (AFP+ VASC–)	RPLND performed	3
Intermediate risk (AFP+ VASC+)	Surveillance	3
Intermediate risk (AFP– VASC–)	Surveillance	5
Intermediate risk (AFP+ VASC+)	Chemotherapy	1*
Intermediate risk (AFP– VASC–)	Chemotherapy	1*
High risk (AFP– VASC+)	RPLND performed	2*
Total		16

*Not considered evaluable for risk assessment regarding relapse.

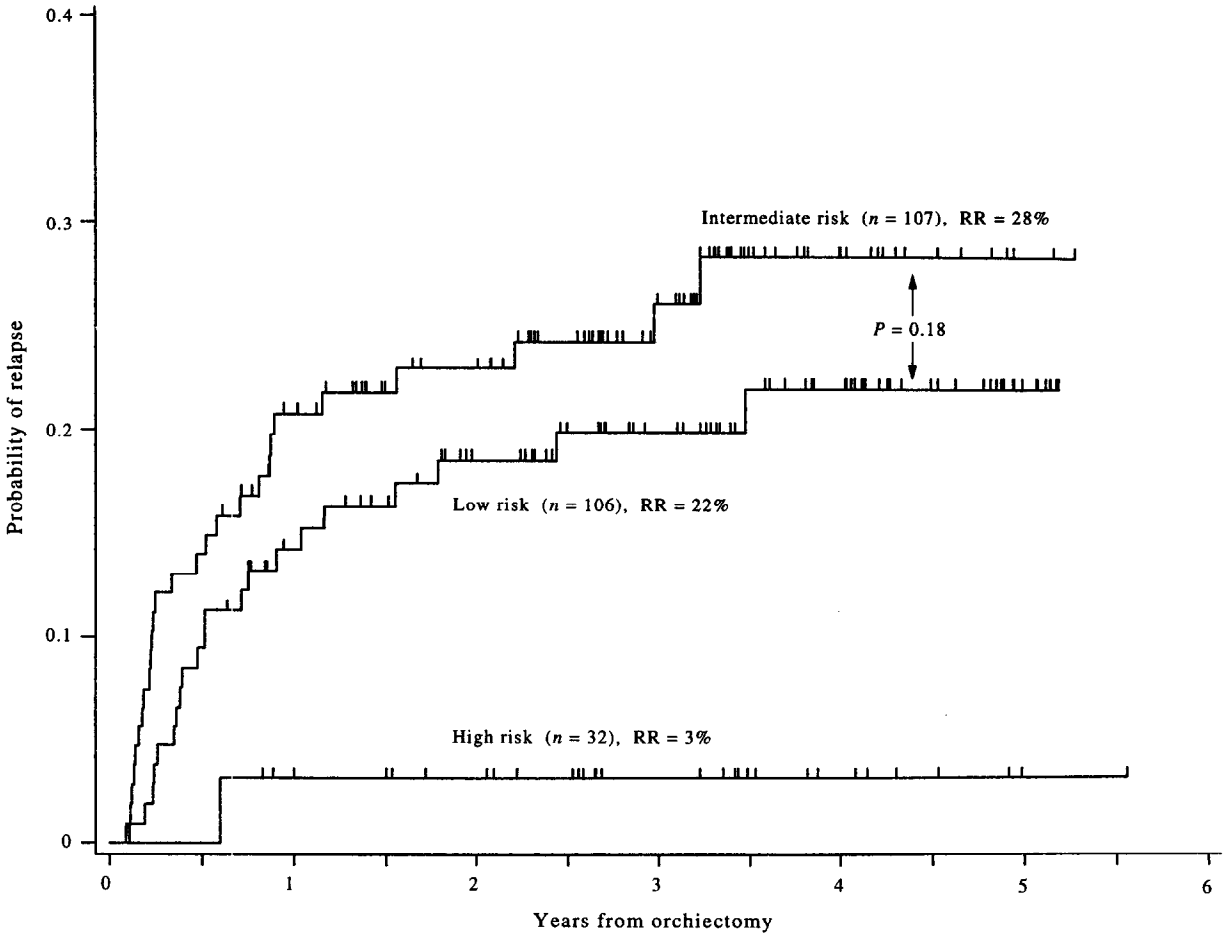

Figure 2. The actuarial relapse rates calculated from the date of orchiectomy for the 245 patients considered evaluable, according to their risk strata. PS2 disease found at staging RPLND is counted as a relapse at the date of RPLND.

retroperitoneal disease at the time of relapse was 25 mm (5–52 mm) and only 2 had retroperitoneal metastases >30 mm. Three patients had (clinically significant at repeated measurements) increased serum tumour markers as the only sign of relapse. 13 out of 20 (65%) of the relapsing low-risk patients had an elevated serum AFP at the time of relapse, and one had elevated serum HCG (human chorionic gonadotrophin) but normal AFP. Thus, 14 (70%) of 20 patients had pathological serum AFP and/or HCG levels at the time of relapse. 6 (38%) out of 16 evaluable patients had elevated serum lactate dehydrogenase (LDH) at the time of relapse and two of these had normal serum AFP and HCG levels.

Intermediate-risk patients. Of the 109 intermediate-risk (IR) patients, 2 received adjuvant chemotherapy instead of staging RPLND and are not evaluable for patterns of relapse (neither of these two relapsed). 8 of the IR patients did not undergo RPLND, but were closely observed similar to the low-risk patients. These 8 IR patients are considered evaluable for relapse rates, but not for pathological staging. 14 (14%) of the 99 IR patients who underwent staging RPLND had PS2 disease. There was no significant difference in regard to PS2 disease at RPLND between the evaluable patients with (VASC+) or without (VASC–) vascular invasion: 5/41 (12%) of the VASC+ and 9/58 (16%) of VASC– patients had PS2 disease. None of the 14 IR patients with PS2 disease relapsed after adjuvant chemotherapy. 13 of the 85 IR patients with PS1 relapsed after RPLND with an actuarial relapse rate of 18%. The risk of relapse despite PS1 at RPLND was significantly (logrank $p = 0.01$) higher for patients with VASC+ (relapse rate 33%) than for PS1 patients with VASC– (relapse rate 7%) (Figure 3). 6 of the IR PS1 patients relapsed in lung, 1 in the abdomen, 3 in the pelvis (one in his left seminal vesicle), 2 in inguinal nodes and 1 had only serum HCG elevation as a sign of relapse. There was no serious or life-threatening complications to RPLND. 4 (6%) out of 70 evaluable PS1 patients had dry ejaculation after RPLND.

Table 3. Distribution of the risk factors used for treatment stratification in the 245 patients considered evaluable for risk assessment

Risk group	No. of patients	VASC–	VASC+	AFP–	AFP+
Low	106	106	—	—	106
Intermediate	107	63	44	63	44
High	32	—	32	32	—
Total	245	169	76	95	150

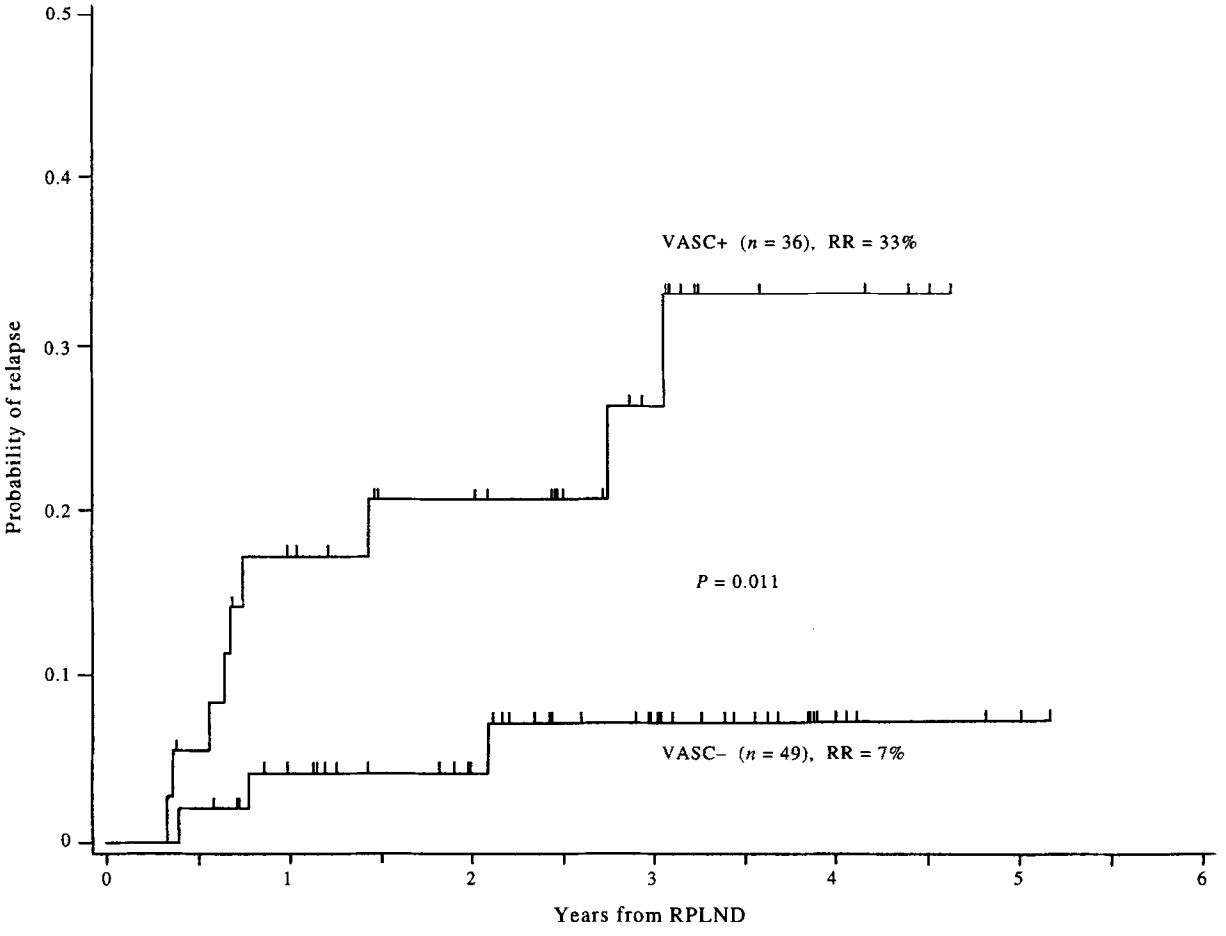

Figure 3. The actuarial relapse rates after staging RPLND for the 85 patients with pathological stage 1 disease, according to the presence (VASC+) or absence (VASC–) of vascular invasion.

High-risk patients. 2 of the 34 high-risk patients underwent staging RPLND and received no adjuvant chemotherapy (both had PS1, one relapsed), the other 32 received adjuvant chemotherapy (PEB × 3). One of 32 (3%) HR patients relapsed with a resectable retroperitoneal mature teratoma 9 months after completion of adjuvant chemotherapy, all others remain free of disease. The patient with a relapsing/growing mature teratoma despite adjuvant chemotherapy did not receive any further chemotherapy after resection and is free of disease 3 years after the resection. There were no serious side-effects of the adjuvant chemotherapy.

Effects of VASC and pre-orchiectomy serum on AFP elevation

The relapse rates (RR) were not significantly different (logrank $p = 0.18$) between the 106 LR (RR = 22%) and all the 107 evaluable IR patients (RR = 22%, Figure 2). The relapse curves for the 106 LR patients with VASC– AFP+ and for the 62 IR patients with VASC– AFP– completely overlapped if the more rapid detection of relapse (in the form of PS2 disease) by staging RPLND was taken into account (Figure 3). The IR patients with VASC+ who did not receive adjuvant chemotherapy had an actuarial relapse rate of 41%, significantly ($p = 0.03$) different from the VASC– patients (Figure 4).

DISCUSSION

The overall therapeutic outcome, with a crude survival and cure rate (so far) of 100%, in 250 consecutive patients with NSGCT included from 18 different hospitals is very encouraging. It should be noted that many of the patients had long distances (often more than 400 km) to travel for follow-up visits in the sparsely populated Swedish and Norwegian rural regions. The good co-operation and secretarial infrastructure within the SWENOTECA group are probably important factors, for the favourable therapeutic outcome even if many of the participating urological and oncological units are comparatively small [7]. The overall rate (22%) of metastatic disease/relapse for clinical stage patients is significantly lower in this study than in the first SWENOTECA study (38%). The important prognostic information gained by a simple histological evaluation of whether malignant cells infiltrate vascular structures in or near the primary tumour was once again illustrated. There was no central review of the histopathological specimens, but the frequency of VASC+ was identical (31%) between the Swedish and the Norwegian hospitals and very near the 28% frequency of VASC+ found in an earlier SWENOTECA study [3].

Three adjuvant courses of PEB chemotherapy are effective in preventing relapse in presumably high-risk patients, but one should be aware of growing teratoma after such

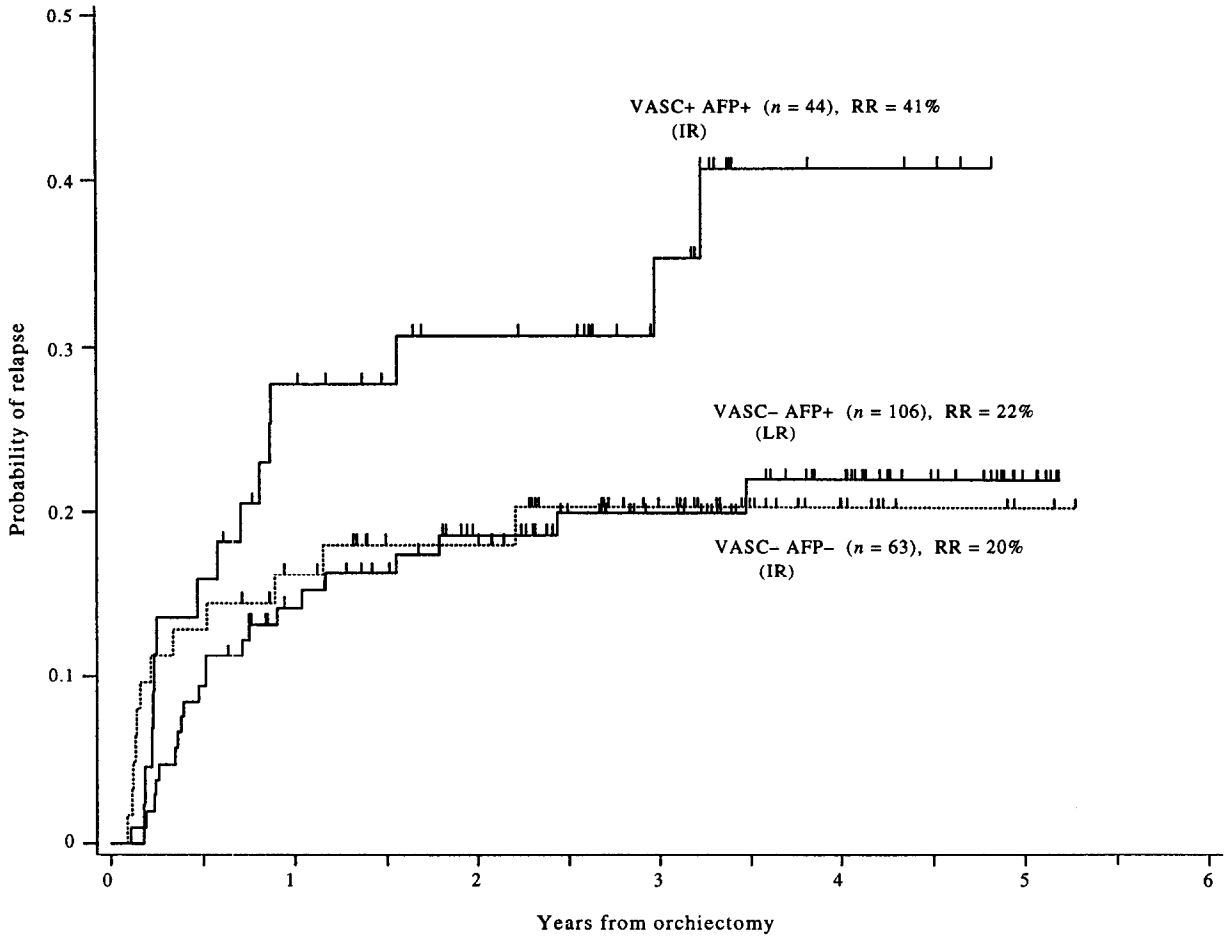

Figure 4. The actuarial relapse rates in LR and IR patients according to the two risk factors. VASC+ is vascular invasion in the primary tumour, AFP+ is serum AFP elevation at orchiectomy. $p = 0.03$ VASC + AFP+ versus VASC − AFP + /AFP − .

treatment, as demonstrated in this study and as reported by Pont and associates [6]. The potentially increased risk of inducing drug-resistant tumour cells and the carcinogenic potential of adjuvant chemotherapy must also be kept in mind. The choice of three full courses of PEB was based upon concern regarding a potentially increased risk of retroperitoneal relapse in NSGTC patients who had not undergone a complete and radical bilateral RPLND, influenced by the findings of Williams and associates [10]. Three courses of PEB chemotherapy may represent overtreatment in an adjuvant setting, as some studies published after the start of our programme reported good results after only two cisplatin-based courses for high-risk NSGTC1 patients [6, 11]. Madej and Pawinski [12] also used three adjuvant courses for high-risk NSGCT1.

The frequency of PS2 disease at staging RPLND was surprisingly low (14%) in the IR patients, where we had expected a rate of approximately 30% based upon our previous experience [3]. Possible explanations may be better pre-RPLND staging, especially our fixed 6-week period of close monitoring of the patient's serum tumour marker levels, and a repeated CT scan just before the planned RPLND. Another explanation may be that a more limited (nerve-sparing) staging RPLND is performed now, with increased risk of missing microscopic retroperitoneal disease. The one retroperitoneal (periaortic) and two of the three pelvic relapses seen in PS1 patients may also be due to the more limited staging RPLND performed in this SWENOTECA study. It is also possible that just the clinical stage 1 patients with VASC+ and without AFP-producing primary tumours, who we considered as high-risk patients are at a higher risk of having retroperitoneal metastases, compared to those with the AFP-producing metastatic tumour cells who will be more easily revealed by persistent serum AFP elevation during clinical staging and before staging RPLND. This was the main rationale for giving these presumed high-risk patients adjuvant chemotherapy. It is possible that we selected the right patients for this effective treatment. We found no convincing prognostic effect of the pre-orchiectomy serum AFP status for clinical stage 1 patients with NSGCT in this study. Patients with AFP and/or HCG-producing primary tumours may be more safely followed up, as there may be a good chance (70% in this study) of an early warning of relapse by serum marker elevation. LDH is also a simple and useful blood test for monitoring NSGCT patients after primary therapy and may possibly indicate a dominance of seminomatous elements in the metastases if the AFP and HCG levels are normal at the time of relapse.

NSGCT1 patients with no vascular invasion by tumour cells in their testis (VASC−), as reported by routine histopathological examination, have only approximately a 20–22% risk of relapse (Figure 4), and nearly all relapsing patients will be cured by salvage chemotherapy. NSGCT1

patients with VASC+ will have at least 40% risk of developing metastatic disease. Most of these VASC+ patients who have subclinical metastases at the time of clinical staging will need chemotherapy, even if approximately 25% of them theoretically may be cured by RPLND alone. A meticulous, but nerve-sparing RPLND will seldom cause ejaculatory disturbances and may reduce the need for abdominal CT or ultrasound examinations in the follow-up period. It is now the consensus among the urologists and oncologists participating in the SWENOTECA co-operative group that the present benefits of routine staging RPLND do not outweigh the (potential) side-effects and the costs related to such a major operation, considering the relatively low frequency of PS2 disease and the persistent risk of relapse for PS1 patients.

We have not performed formal comparative quality of life or cost utility studies between the three available options for NSGCT1 patients, i.e. surveillance, pathological staging by RPLND or adjuvant chemotherapy, but these will be important topics for further studies. Based upon the present and previous SWENOTECA studies and the experience of other investigators, we will use only vascular invasion for risk stratification in a new SWENOTECA study (recently initiated). Clinical stage 1 patients with VASC+ will be offered two adjuvant courses of cisplatin, vinblastine and bleomycin (CVB) as our preferred treatment option. Patients with VASC– will be invited to participate in a randomised study to compare surveillance versus one course of CVB. A non-etoposide containing adjuvant chemotherapy will be used in order to avoid or reduce the risk of leukaemia in this patient population with a very favourable prognosis [8]. Patients who, after being thoroughly informed, decline to receive our standard (or randomised) option, will be able to freely choose between surveillance or 1–2 courses of adjuvant CVB chemotherapy, but with an emphasis on surveillance.

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