Multicentre risk-adapted management for stage I non-seminomatous germ cell tumours


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Background: The Spanish Germ Cell Group is composed of 60 centres. Our challenge was to define a surveillance protocol that would be safe and suitable regardless of population size or geographic coverage.

Methods: From January 1994 to January 2004, 589 patients with stage I non-seminomatous germ cell tumours entered a risk-adapted surveillance protocol after orchiectomy. Patients with vascular or local invasion of adjacent structures (231/589; 39%) received two cycles of BEP (bleomicin 30 U/week, etoposide 100 mg/m² ×4, cisplatinum 25 mg/m² ×4). Other patients (358/589; 61%) were kept on close follow-up (chest X-ray; serum tumour markers: first year every 2 months, second year every 3 months, third year every 4 months; abdominal computed tomography scans at every other outpatient control). The outcomes selected for the study were feasibility, relapse rate and number of patients lost to follow-up and mortality.

Results: Median follow-up was 40 months. In the surveillance group, 21 patients were lost to follow-up. In the chemotherapy group, two patients relapsed at 12 and 14.5 months and they are presently free of disease. In the surveillance group, 71 (19%) patients relapsed, of which 55 (71%) relapsed within the first year. Five (1.4%) patients died of their cancer. Factors associated with relapse were embryonal carcinoma and vascular invasion in patients who refused chemotherapy.

Conclusions: Our risk-adapted surveillance protocol provided a low rate of recurrences.

Key words: non-seminomatous germ cell tumours, stage I, risk-adapted surveillance

Introduction

The management approach for stage I testicular germ cell tumours (TGT) varies between centres and countries. Experience from stage IIb TGT shows that two cycles of adjuvant chemotherapy after retroperitoneal lymph node dissection are sufficient to prevent recurrences [1]. There appears to be no difference in survival between surveillance and adjuvant treatment, and the total adjuvant therapy dose is lower than the standard dose at relapse. This is an important issue for patients with a high risk of recurrence [2]. In the setting of localised disease, adjuvant treatment has proved to reduce relapses to less than 5%, and results are quite consistent regardless of the size of the trial or the country [3–11]. An argument against adjuvant chemotherapy is the fact that only 30% of patients present positive nodes after a retroperitoneal dissection. Known risk factors for relapse in stage I TGT are vascular invasion and embryonal carcinoma [12]. Patients with vascular invasion have a relapse rate of about 40%, whereas in patients without venous or lymphatic invasion, the relapse rate drops below 20%. If we avoid relapse in patients with vascular invasion by means of adjuvant chemotherapy, the rate of recurrence may drop to less than 15% providing there is close surveillance of patients with a lower risk of relapse.

With a long experience in this setting [13], the Spanish Germinal Group [14] designed a risk-adapted surveillance protocol with adjuvant chemotherapy guided by known risk factors for use in a multicentre setting to reduce the relapse rate and avoid retroperitoneal lymphadenectomy.

Patients and methods

Between January 1994 and January 2004, 589 newly diagnosed patients with clinical stage I (T1–T4) (1987 TNM classification) non-seminomatous TGTs of the testis following orchiectomy were entered in a prospective risk-adapted surveillance protocol. Two cycles of BEP (bleomicin, etoposide, cisplatinum) were recommended if vascular invasion was identified and/or if embryonal carcinoma was observed between 1994 and 1996. Chemotherapy was initiated between 4 and 8 weeks after orchiectomy. Clinical staging was based on history, physical examination, post-orchiectomy serum tumour markers (α-fetoprotein, β-human chorionic gonadotropin and lactic dehydrogenase), and computed tomography (CT) of the thorax, abdomen and pelvis. Criteria for inclusion in the follow-up protocol were unequivocal
absence of any clinical evidence of metastases, including negative serum tumour markers post-orchiectomy.

Histopathological review included tumour size, pathological stage (T1–T4), histological pattern, predominant histological subtype and determination of the presence or absence of vascular invasion. By the term ‘main histology’, we mean the pattern that involved 50% or more of the tumour. We excluded patients with pure choriocarcinoma or pure seminoma, and those who were unreliable for close follow-up.

Patients who refused chemotherapy were also included in the analysis as part of the surveillance group.

Definition of vascular invasion

Vascular invasion was defined as: (i) compact aggregation of tumour cells within a blood-vessel lumen similar to or associated with thrombotic occlusion; and (ii) definite endothelial destruction by tumour invasion.

Follow-up

The patients were carefully followed according to an established protocol. They were seen at 2-monthly intervals for year 1, every 3 months for year 2, every 4 months during year 3 and every 6 months thereafter, and for at least 6 years, but a 10-year period was recommended. Serum tumour markers and chest X-ray were obtained at each visit and CT of the abdomen and pelvis was performed at every other outpatient visit. Patients with disease recurrence were treated with chemotherapy and/or surgery.

Statistical analysis

The study was designed as an observation trial and patients were analysed as treated; patients on follow-up were analysed together regardless of the presence or not of vascular invasion. All patients who received chemotherapy presented at least one of the risk factors mentioned above [vascular invasion, embryonal carcinoma or local invasion of adjacent structures (T >T2)].

Statistical analysis was performed with SPSS statistical software, version 11.52. Relapse-free survival curves were computed using the Kaplan–Meier method. Univariate analysis of prognostic factors for relapse was performed using the log-rank test and Wilcoxon statistics. Factors included in the multivariate analysis were age, histological pattern (presence or absence of embryonal carcinoma, presence or absence of teratomatous elements), pre-surgery levels of serum tumour markers, vascular invasion, size of tumour and invasion of surrounding structures.

Adjuvant treatment

Two hundred and thirty-one patients (39%) received chemotherapy. Treatment consisted of two cycles of BE400P (bleomicin 30 U/week, etoposide 100 mg/m² and cisplatinum 25 mg/m² days 1–4). Nineteen patients with vascular invasion received just one cycle of BEP within a pilot study in a single centre and they were included in the chemotherapy group [15].

Criteria for treatment

These included histological evidence of local invasion of adjacent structures beyond the albuginea, or vascular invasion. Patients with embryonal carcinoma as the only risk factor were included for treatment only in the first 2 years of the study; after this time chemotherapy was not recommended.

Assessment of toxicity

All patients were evaluated for acute chemotherapy-related toxicity using the World Health Organisation toxicity grading system. Fatherhood was recorded, as well as incidence of second tumours, including contralateral testis cancer.

Results

Patients’ characteristics are summarised in Table 1. Median size of tumour was 3.5 cm (range 0.3–15). Three patients had invasion of the scrotum and 11 invasion of the spermatic cord. Vascular invasion was identified in 175 patients. Overall, 408 patients (69%) were T1 tumours. Mixed histology was frequent. Among the predominant patterns, embryonal carcinoma was that most frequently reported (316 patients; 53%). The flow chart in Figure 1 illustrates the distribution of patients by treatment group (surveillance or chemotherapy) and relapses. Figures 2 and 3 illustrate disease-free and overall survival for all the patients included in the study.

Patients on surveillance alone

A total of 358 patients did not receive adjuvant chemotherapy. Two hundred and eighty-seven patients (80%) were continuously free of disease for a median of 48 months following orchiectomy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median 26.4</td>
</tr>
<tr>
<td></td>
<td>Range 15–60</td>
</tr>
<tr>
<td>Cryptorchidia</td>
<td>49 (0.8)</td>
</tr>
<tr>
<td>Location [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>275 (45)</td>
</tr>
<tr>
<td>Right</td>
<td>314 (55)</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>Median 3.5</td>
</tr>
<tr>
<td></td>
<td>Range 0.3–15</td>
</tr>
<tr>
<td>Pre-orchiectomy serum tumour markers, U/l [median (range)]</td>
<td>27 (0–29340)</td>
</tr>
<tr>
<td>β-HCG</td>
<td>5 (0–8310)</td>
</tr>
<tr>
<td>T</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>408</td>
</tr>
<tr>
<td>T2</td>
<td>167</td>
</tr>
<tr>
<td>T3</td>
<td>11</td>
</tr>
<tr>
<td>T4</td>
<td>3</td>
</tr>
<tr>
<td>Vascular invasion [n (%)]</td>
<td>175 (30)</td>
</tr>
<tr>
<td>Histology: main pattern [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>316 (53.3)</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>78 (13)</td>
</tr>
<tr>
<td>Seminoma</td>
<td>74 (13)</td>
</tr>
<tr>
<td>Mature teratoma</td>
<td>54 (9)</td>
</tr>
<tr>
<td>Yolk sac</td>
<td>57 (9)</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>3 (0.5)</td>
</tr>
</tbody>
</table>

HCG, human chorionic gonadotropin.
and 71 had relapse. Relapses occurred within 1–40 months, including 35 cases within 6 months, following orchiectomy (Figure 4). Five patients relapsed after the second year of follow-up.

Ten-year disease-free survival was 84.7% [95% confidence interval (CI) 81% to 88.4%]. In the majority of cases relapses occurred in the retroperitoneal lymph nodes only.

Five (1.3%) patients died: three patients had late relapses (at +24, +30 and +42.5 months, and died at +100, +40 and +61 months, respectively). All of them were patients with tumours with good prognosis. One patient was diagnosed as having AIDS and died during chemotherapy in his first relapse (+8.5 months), and another patient had refractory disease at relapse and died at +13 months. Ten-year disease-specific survival was 95% (95% CI 90% to 99%).

Predictors of relapse. The strongest predictors of recurrence in univariate and multivariate analysis (Figures 5 and 6) were vascular invasion (22 patients on surveillance) and embryonal carcinoma (164 patients). The risk of recurrence was higher when the main histology was embryonal carcinoma, with a 5-year disease-free survival of 66.59% (95% CI 58.5% to 74.5%) versus 82.52% (95% CI 75% to 90%) (P < 0.001) when embryonal carcinoma was the second pattern and 88.1% (95% CI 80% to 96%) if embryonal carcinoma was not detected at all (Figure 5). Vascular invasion was also a significant predictor of recurrence.
Those patients who refused the recommended treatment and chose surveillance despite vascular invasion had a higher rate of relapse [5-year disease-free survival of 39.6% (95% CI 26% to 50%) versus 79.5% (95% CI 75% to 85%); \( P < 0.001 \)].

Size, age, pre-orchiectomy serum α-fetoprotein and β-human chorionic gonadotropin level had no predictive value in the multivariate analysis (Table 2).

**Patients who received adjuvant chemotherapy**

Chemotherapy was initiated because of invasion of local structures in 11 cases (4%), vascular invasion alone in 15 (6%), for embryonal carcinoma as the main histology in 67 (29%), and vascular invasion and embryonal carcinoma in 138 (60%).

Only two patients in this group relapsed, at 12 and 15 months from orchiectomy. Both relapses were in retroperitoneal nodes and surgical resection was performed. One of the two showed only mature teratoma and the second an embryonal carcinoma, i.e. only one patient relapsed with viable tumour. He received three cycles of second line VIP (vinblastine, ifosfamide, cisplatinum) chemotherapy. Both patients are presently disease-free.

Overall survival is 100%.

**Toxicity**

**Haematological toxicity.** Toxicity of BE\(_{400}\)P was moderate. Grade III–IV toxicity was infrequent. Neutropenia grade III–IV was detected in 27% of patients, generally without clinical significance. Grade III thrombopenia occurred in 1% of patients. There were no treatment-related deaths.

**Non-haematological toxicity.** Grade III–IV nausea and vomiting affected only 4% of patients. One patient had a severe reaction to bleomycin and treatment was withdrawn.

**Fatherhood.** Cryopreservation was available for all patients before chemotherapy. To date, 19 patients treated with chemotherapy...

![Figure 4](image-url). Surveillance: timing of recurrences. Dark grey column, absolute number of relapses per period; light grey column, percentage of relapses per period.

![Figure 5](image-url). Patients under surveillance. Kaplan–Maier survival by prognostic factors. Embryonal carcinoma (\( P < 0.001 \)). *Three groups with: embryonal carcinoma as the main histology (lower line), second predominant pattern (central line) and absence (upper line).

![Figure 6](image-url). Patients under surveillance. Kaplan–Maier survival by prognostic factors. Vascular Invasion (\( P <0.001 \)). *Upper line, no vascular invasion; lower line, vascular invasion.

**Table 2.** Patients under surveillance: results of the multivariate Cox model for disease free survival

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>RR</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Embryonal carcinoma</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main component</td>
<td>2.998</td>
<td>1.5–5.98</td>
<td>0.002</td>
</tr>
<tr>
<td>As secondary pattern</td>
<td>1.612</td>
<td>0.7–3.68</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Vascular invasion</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>3.398</td>
<td>1.8–6.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absence</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Size (&lt; or &gt;4 cm)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>α-fetoprotein (&lt;1000, 1000–10 000, &gt;10 000 mg/dl)</em></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval; NS, not significant.
have fathered a child, all but one without using cryopreserved semen.

Contralateral tumours and incidence of second neoplasms following orchidectomy

We analysed the incidence of testicular and other tumours in our cohort of patients following inclusion in the study, with a median follow-up of 42 months. Eight (1.3%) patients developed a tumour affecting the contralateral testicle; in four this was a synchronous tumour and in the other four it was a metachronous tumour diagnosed between +60 and +96 months.

One patient was diagnosed with non-Hodgkin lymphoma 5 years after the testicular tumour was detected, and one with Hodgkin disease 3 years after orchidectomy. Neither of them had received chemotherapy.

Lost to follow-up

Overall, 21 (4%) of 589 patients were lost to follow-up. Under surveillance, 12 (3%) of 358 patients did not complete a minimum of 5 years of follow-up; only six did not continue follow-up for at least 2 years and none for <1 year. Nine patients who received chemotherapy were lost, three within the first year and six within the second year.

Discussion

Cisplatinum-based chemotherapy has changed the management of metastatic TGTs, dramatically improving overall survival. Presently, diminishing morbidity of treatment and maintaining efficacy should be an objective for patients and physicians in the setting of this curable neoplasm. How can we include highly effective chemotherapy in the management of stage I tumours without increasing morbidity? Retroperitoneal lymphadenectomy provides pathological staging and it may be curative, but only 30% of patients will show positive results. Even with surgeons with long experience, 3% of patients may have a major complication, and chemotherapy is not always avoided. Moreover, close follow-up of patients with positive lymph nodes is important because 12% of them will relapse [16].

Surveillance alone has drawbacks. Patient compliance may be poor and for all patients it causes significant anxiety or ‘Dancees syndrome’ [17]. Especially in a multicentre setting, maintaining a low rate of relapse is mandatory considering the risk of poor compliance, which is always a problem in young patients, where psychological factors play an important role. Adjuvant treatment stratified by risk factors is another choice. Decreasing relapse by adjuvant chemotherapy in patients at highest risk would reduce the number of relapses in the total patient group. Factors associated with recurrence are absence of yolk sac elements, presence of undifferentiated cells or embryonal carcinoma [18], and capillary or lymphatic invasion [19]. Vascular invasion seems the strongest predictor of recurrence and we chose it for stratification [20]. The objective of our group was also to limit treatment, i.e. treat the minimum number of patients and with the minimum effective doses. To accomplish this objective, we initially recommended chemotherapy if embryonal carcinoma and/or vascular invasion were present. Two years later, we selected only patients with vascular invasion for treatment. Although the majority of relapses occurred in patients with embryonal carcinoma in the group of surveillance, if we expanded the criteria for treatment to include embryonal carcinoma, a further 150 patients would have been treated. This would probably imply overtreatment for stage I patients and may preclude the advantage of a risk-adapted protocol. In our study, only 71 patients under surveillance relapsed, and 12 of these should have been treated owing to the presence of vascular invasion. However, these patients refused chemotherapy. Therefore, only 59 patients would have relapsed if criteria had been adequately applied. Surveillance for patients without vascular invasion should be sufficient to detect recurrences in time for successful treatment. Our results also suggest that patients undergoing chemotherapy need not be followed so strictly.

We treated 231 patients, 39% of the total group, and delivered a total of 462 cycles of chemotherapy. We cannot avoid treating some patients possibly cured with orchietomy alone, but in a multicentre setting, this policy may avoid relapses that can reduce survival. To limit the long-term impact of chemotherapy, adequate information regarding late toxicity (hypertension, dyslipidemia) and its preventive measures should be addressed to patients. Furthermore, to prevent recurrences, two cycles of chemotherapy were sufficient. We used a total of 800 mg/m² etoposide and 180 IU bleomycin, well below what is considered a dangerous dose [21].

Relapses occurred in the first 24 months of follow-up. Most were in the first 6 months and mainly occurred in retroperitoneal nodes. This finding is consistent with other publications that also reported about 10% of late (more than 2 years) recurrences. In our series, 7% of relapses under surveillance—or 0.5% of the total patient group—occurred after 2 years of follow-up. A more intensive follow-up is thus mandatory during the first 2 years, especially in terms of the frequency of abdominal scans. Hazards related to low-dose radiation cannot be established [22], but it does seem safe to reduce the frequency of CT scans as soon as possible. An open-door policy and adequate information about signs and symptoms may be a better choice.

In addition to late effects, mortality is also a primary concern in a disease affecting young patients. Disease-specific mortality in our series was 0.8%, which is within the range of historical series based on retroperitoneal dissection that reported mortality as high as 1.9% [23, 24]. Adequate information provided a relatively low incidence of losses to follow-up during the high-risk first 2–5 years, and most of the losses occurred after the critical second year. Relapses were detected with a low level of serum tumour markers, but unfortunately three of the five were late relapses, which usually imply a worse prognosis. If a follow-up strategy is chosen, especially in patients with risk factors, it must be strictly adhered to and patients must show a high level of compliance.

In conclusion, at the cost of a low rate of acute toxicity due to chemotherapy, we reduced the total number of relapses in
a non-selected group of stage I patients. Again, when we ana-
lysed prognostic factors for relapse in the group under surveil-
ランス, embryonal carcinoma and vascular invasion were both 
predictors of recurrence. Patients with either of these factors 
had a three-fold risk of relapse. Orchiectomy as the only treat-
ment in patients with histopathological adverse features seems 
insufficient. Adjuvant chemotherapy could be recommended 
after the patient is adequately informed, at least for patients with 
vascular invasion. Although patients with embryonal carcinoma 
have a high risk of relapse, overtreatment may diminish the 
benefit of a risk-adapted protocol that seeks to reduce relapses 
but not augment acute or late toxicities.

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