All patients with stage 1 testicular germ-cell tumours (TGCT) can expect to be permanently cured with currently available management approaches. Orchidectomy alone cures 80% of pure seminomas and 70%–75% of nonseminomatous and combined seminoma plus nonseminomatous germ-cell tumours of the testis (NSGCTT). Currently there are well-validated criteria for estimating recurrence risk in NSGCTT. The presence of vascular invasion (VI+) in the testicular primary identifies a group with a recurrence risk approaching 50%. In VI−cases, the risk is ≤20%. Adjuvant chemotherapy with two cycles of bleomycin, etoposide, and cisplatin (BEP) is increasingly recommended in VI+ cases, and when offered is selected in place of surveillance by many VI−patients. In seminomatous germ-cell testicular tumours (SGCTT), there are no validated criteria for estimating recurrence risk. Concerns about second cancers complicating adjuvant radiotherapy are reducing its popularity and the absence of tumour markers, the need for frequent scans, long follow-up and evidence of poor compliance argue against surveillance. Single-dose carboplatin is well tolerated, cheap, reduces recurrence rates to <5% and also the risk of second primary TGCT. There remain concerns about long-term toxicity although evidence is accumulating to allay these. This article discusses the relevant issues affecting decision-making and choice in these intriguing, curable cancers.

Key words: adjuvant chemotherapy, non-seminoma, seminoma, stage 1, surveillance, testicular cancer

introduction

In Northern Europe, the incidence of testicular germ-cell tumours (TGCT) continues to increase. About two-thirds of all cases present in stage 1 where the cancer is apparently confined to the testis (i.e. over 80% of seminomas and around 50% of non-seminomas). The existence of undetectable micrometastases results in distant recurrence following orchidectomy in about 20% of SGCTT (seminomatous germ-cell testicular tumours) and 25%–30% of NSGCTT (non-seminomatous germ-cell testicular tumours). In the case of NSGCTT, 80% of recurrences occur within 1 year, and >90% within 2 years of orchidectomy [1], whereas for seminomas nearly a third of all recurrences occur after 2 years and 7% occur more than 6 years after orchidectomy [2]. For both the varieties of GCT recurrences can be treated successfully resulting in overall cure rates of about 98%–99%. However, there have been continuing efforts to reduce the recurrence risk with adjuvant therapy following orchidectomy and thus avoid the significant emotional consequences of cancer recurrence, the inconvenience and costs of surveillance and the risks of failed adherence to surveillance by both patients and health care systems [3]. For many years, para-aortic radiotherapy was the favoured adjuvant therapy in SGCTT given that the majority of recurrences were in retroperitoneal lymph nodes, but more recently chemotherapy with single-agent carboplatin has gained popularity. NSGCTT have a greater capacity for haematogenous spread and therefore, adjuvant chemotherapy (ACT) has been much more successful than para-aortic radiotherapy.

management options for stage 1 nonseminomatous germ-cell tumours of testis (NSGCTT)

surveillance

Careful surveillance following orchidectomy first became an option in the 1980s when it was clear that cisplatin-based chemotherapy could rescue nearly all recurrences [4, 5]. This led to the UK Medical Research Council (MRC) studies of surveillance in stage 1 NSGCTT. First, a retrospective analysis of 259 patients was carried out with a detailed histological review [6]. The independent predictors of recurrence were invasion of testicular veins and lymphatics, the absence of yolk sac elements, and presence of undifferentiated tumour. An index based on the number of these features enabled identification of patients at higher risk of recurrence. By far the most important predictors were invasion of testicular veins or lymphatics, i.e. vascular invasion (VI). There is now universal acceptance of VI as the key prognostic factor [7]. This change
increased the 2-year recurrence-free survival of the high-risk group (from 53% to 60%), but also substantially increases the overall proportion of high-risk patients (from <25% to >50%).

There then followed a prospective surveillance study in 373 cases and the validity of the histological index was confirmed [1]. The recurrence rate was 27%. Of these, 80% recurred within the first year. Following treatment for recurrence, 5-year survival exceeded 98%. These data are consistent with other surveillance studies and the survival figures compare favourably with the best series for retroperitoneal lymph node dissection (RPLND) [8]. The Toronto group presented the results of a prospective surveillance study [9] confirming the MRC prospective study. Surveillance programmes varied in their intensity and duration. However in 2007, the results of a randomised trial of computed tomography (CT) scan frequency during surveillance in stage 1 NSGCTT (2 scans versus 5 scans) showed that 2 (at 3- and 12-month post-orchidectomy) were sufficient [10]. The importance of VI as the most important independent risk factor has been emphasized repeatedly in subsequent studies. A systematic review of 23 publications between 1979 and 2001 demonstrated that whereas 29% of 2587 stage 1 patients had occult metastases, among those with VI (36% of the total) the figure was 50%, and with an odds ratio (OR) of 5.2 this was the strongest predictor [11].

disadvantages of surveillance

For some patients, frequent hospital attendance, physical examination, blood tests, and CT scans can be stressful and serve as a constant reminder of their cancer history and ongoing risk of recurrence. In childhood cancers, this has been referred to as the ‘Damocles syndrome’ [12]. Surveillance also depends critically on excellent patient compliance. This can be a problem for young patients who may have a less well-developed sense of responsibility for their own health and there is evidence of poor compliance among stage 1 NSGCTT patients on surveillance [3, 13]. They are more inclined to move to different localities and can experience difficulties with employment, mortgages, life insurance, or adoption whilst undergoing surveillance. Finally, a major drawback to surveillance is that a substantial minority of cases will recur with disease subsequently requiring major surgery (most commonly RPLND) following chemotherapy. In 2005, Link et al. [14] estimated that 20% of patients managed initially with surveillance would eventually require RPLND. In the very important paper on risk-adapted management for stage 1 from the SWENOTECA group [15], 8% of VI-negative (VI–) cases and 33% of VI-positive (VI+) cases managed on surveillance eventually required RPLND. These risks are clearly not insignificant and must be considered when contemplating surveillance as an option. Fewer than 1% of cases managed with ACT ever require RPLND (see below).

ACT for stage 1 NSGCTT

The demonstration of a reliable prognostic index which identified a group at high risk of recurrence provided a clear opportunity for ACT in stage 1 NSGCTT [6]. Short-term tolerance to cisplatin-based chemotherapy decreases with increasing cycle number, and long-term toxicity increases with total dose received. Using chemotherapy in the adjuvant setting would mean that, even in a high-risk (VI+) group, about half the patients would receive unnecessary treatment. It is vital, therefore, to give the minimum treatment required to eradicate the small tumour burden.

Two trials in stage 2 NSGCTT having had primary RPLND suggested that two cycles would be sufficient and acceptable [16, 17]. Thus, the MRC designed a prospective study offering two cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy to patients with high-risk stage 1 NSGCTT [18]. The aim of the study was to evaluate the efficacy and long-term toxicity of ACT. Recurrence and survival were expected to approach 100% and if randomisation to surveillance had been adopted the numbers required to show a survival difference (or equivalence) would have been prohibitive. Furthermore, the MRC surveillance studies had given consistent and robust figures for recurrence. Consequently, a non-randomised study was proposed, but with close monitoring and strict stopping rules (which would have been required in any case in a randomised trial) should the recurrence rate exceed 5%. The 2-year recurrence-free survival in 114 cases was 98%. The 95% confidence interval (CI) excluded a true recurrence rate of >5%. Of the two patients who recurred, one had adenocarcinoma of the rete testis rather than a GCT on histological review. Long-term toxicity was assessed by pre- and post-treatment analysis of renal function, lung function, semen analysis, and audiometry. No major, clinically significant changes were observed. This demonstrates that the major toxic effects associated with BEP chemotherapy (renal, lung, hearing, fertility) were mild or absent following two cycles.

alternative adjuvant regimens

Minimising toxicity is important in all ACT studies. Accordingly, trials have evaluated alternatives to BEP. The substitution of BOP for BEP chemotherapy, in which etoposide was replaced by vincristine [19], resulted in no gain in toxicity although efficacy was retained. Similarly replacing cisplatin with carboplatin has been discarded since, despite optimistic conclusions, the occurrence of two deaths from chemotherapy-resistant disease in 52 cases casts doubt upon the safety of this approach [20]. The inferior results of carboplatin versus cisplatin in good prognosis metastatic NSGCTT [21] have reinforced concerns over this substitution as an adjuvant therapy, and BEP remains the preferred choice.

These studies demonstrated the use of adjuvant BEP chemotherapy to be a safe and effective approach in the management of high-risk stage 1 NSGCTT. Since cure is not guaranteed patients are still monitored for 5 years. However, a much less intensive surveillance programme can be adopted for patients with recurrence-free survival of 98% at 2 years.

short-term toxicity of BEP chemotherapy

The acute side-effects of BEP chemotherapy are well known. Neutropenic sepsis is a frequent complication of testis tumour chemotherapy and is still occasionally fatal. In the UK trial demonstrating the efficacy of prophylactic levofloxacin [22],
tests tumour patients had by far the highest risk of neutropenic sepsis (almost 30%) among solid tumours. This was almost exactly the same figure as that reported in an earlier EORTC/MRC trial of prophylactic granulocyte colony stimulating factor (GCSF) [23]. Half of all febrile episodes occur with the first cycle of chemotherapy and, where there are concerns about over exposure to antimicrobials, limiting prophylaxis to the first cycle only may be considered [24]. There is now meta-analysis evidence that prophylactic fluoroquinolones reduce all-cause, 30-day mortality when used following myelosuppressive chemotherapy in solid tumours [25]. The GCSFs also reduce febrile episodes and both fluoroquinolones and GCSF together seem more effective than either alone [26].

**long-term toxicity of BEP chemotherapy**

Long-term toxicity is particularly important in diseases of younger people, but clearly data take a long time to emerge.

- Fertility. Since the introduction of effective chemotherapy, there have been a number of reports examining fertility [7, 27, 28]. However, semen analysis and rates of patients who fathered a child were available in only a minority of patients before and after treatment. Hence, the conclusion that ACT has no long-term effect on fertility, is based on small numbers. The German Testicular Cancer (TC) Study Group has reported on 93 patients with follicle-stimulating hormone (FSH) values and 58 patients with sperm analysis during follow-up after treatment of clinical stage I NSGCTT. In summary, about two-thirds of patients already had substantial pre-treatment abnormality of fertility values. Hence, a negative impact of two cycles of adjuvant BEP on post-treatment fertility was not shown [28]. Patients about to receive adjuvant BEP should be offered sperm banking.

- Cardiovascular events. There have been a number of studies which report a moderate but significantly increased risk of cardiovascular disease (CVD) in TC survivors after treatment with either chemotherapy [29], radiotherapy [30], or both [31]. These studies had several limitations; the numbers of cardiac events were small, validation of events was limited, and/or data on primary treatment of individuals were lacking. A more recent study among 2512 five-year survivors of TC showed a 3.7-fold increased myocardial infarction (MI) risk following mediastinal irradiation compared with surgery alone and a 1.9-fold increased MI risk following PVB plus maintenance chemotherapy given pre-mid 1980s. BEP with no maintenance chemotherapy was associated with a borderline increased risk of CVD but no significant increase in MI [32]. This highlights a key difficulty with long-term follow-up studies which necessarily focus on patients who received outdated treatments. Throughout the last two decades, the duration and total doses of chemotherapy administered have declined progressively. This is clearly reflected in late toxicity. So patients receiving >850 mg total dose of cisplatin (equivalent to ≥5 cycles of BEP) were recently shown to have an increased calculated risk of developing fatal CV events, whilst those receiving <850 mg did not [33].

- Metabolic syndrome. The mechanism for these effects on CVD is not known but two recent reports [34, 35] suggest that it might be through development of the so-called metabolic syndrome (insulin resistance, hypertension, dyslipidemia, and abdominal obesity), which is associated with CVD. Unfortunately, the definition of metabolic syndrome (MS) in the two studies was different and the results are inconsistent. In the Dutch study [34], 9% of controls (healthy age-matched men) had MS, compared with 26% of chemotherapy-treated TC patients (P = 0.017), but interestingly 36% of stage 1 TC patients treated with orchidectomy alone had MS (P = 0.002). The authors suggested that gonadal dysfunction might be the link. In the Norwegian study [35], where the OR for MS in healthy controls was set as 1, the OR in surgery-only cases was 0.67, surgery plus radiotherapy was 0.76, cisplatin ≤850 mg it was 0.99 but in cisplatin >850 mg it was 2.16 (significantly higher than controls and surgery-alone cases).

**guidelines for stage 1 NSGCTT**

The clear efficacy of two cycles of adjuvant BEP (etoposide total dose 360 mg/sqM) has been confirmed in smaller single-group studies and adopted as a standard practice in many centres across the world. It is the recommended treatment in the Scottish Intercollegiate Guidelines Network guidelines 1998 (Scotland), the Clinical Oncology Information Network (UK) guidelines 2000 (England), the ESMO guidelines 2008 and the European Consensus Conference on Diagnosis and Treatment of Germ-Cell Cancer 2008 (Europe), and the National Comprehensive Cancer Network guidelines 2008 (USA). However, RPLND is still practised in some countries, and surveillance is favoured in others.

**a single cycle of BEP**

Following the failure of drug substitutions to convincingly reduce the toxicity of ACT, the next step was clearly to examine a single cycle of full dose (etoposide total dose 500 mg/sqM) BEP [36–40]. Very encouraging results were reported in two European studies:

**German TC study AH 01/94**

In this trial, 382 patients with stage 1 NSGCTT were randomly assigned between RPLND and one cycle of adjuvant BEP [40]. The primary end-point was recurrence rate. There were 347 eligible cases treated according to the protocol and the median follow-up time was 4.7 years. Fifteen patients (7.9%) relapsed following RPLND and 2 (1.0%) after BEPx1 (P = 0.0011). The difference in the 2-year-recurrence-free survival rate between chemotherapy [99.5%, 95% CI (96.2% to 99.9%)] and surgery [91.9%, 95% CI (86.9% to 95.0%)] was 7.6, 95% CI 3.1% to 12.0%. The hazard ratio (HR) for tumour recurrence with surgery versus chemotherapy was 7.9, 95% CI 1.8–34.5. The rate of in-field retroperitoneal relapses was higher than expected from single centre experiences in this multi-centre trial.

The rate of VI+ was 42% in both the groups. Hence, neither of the two treatment arms reflect standard practice in the UK and much of the rest of the world where surveillance is preferred for low-risk patients, and where RPLND has been
The Swedish and Norwegian TC project (SWENOTECA) From 1998 to 2005, 745 Norwegian and Swedish patients with stage 1 NSGCTT were included in a prospective, community-based multicenter management program [15]. Treatment strategy depended on the presence or absence of VI. VI+ patients were recommended ACT and could choose one or two cycles of BEP, whereas VI− patients could choose between ACT (one cycle) and surveillance. At a median follow-up of 4.7 years, there had been 51 relapses. Among the 239 VI+ cases, 157 (66%) chose one cycle and 70 (29%) chose two cycles. The remaining 12 cases received no adjuvant therapy for a variety of reasons (e.g. protocol violations/comorbidities). There were 495 VI− cases and 338 (68%) of these selected no adjuvant therapy whilst 155 (31%) chose BEP x1 and 2 had BEP x2.

On surveillance, 41.7% of VI+ patients relapsed, compared with 13.2% of VI− patients. After one course of BEP, 3.2% of VI+ and 1.3% of VI− patients relapsed. The toxicity of adjuvant BEP was low. Eight patients had died, none from progressive disease. It is also important to note that almost 1/3 of VI− cases opted for ACT. Also, it is noteworthy that 33% of VI+ cases and 8% of VI− cases managed on surveillance eventually required RPLND.

As a result, SWENOTECA currently recommends one course of BEP as standard treatment of VI+ CS1 NSGCTT, whereas both surveillance and one course of BEP are options for VI− patients.

Birmingham testicular tumour service [41]
In the 10 years between 2000 and 2009, our centre in Birmingham which currently serves a population of 1.88 m males (the catchment area has steadily increased during this period) has treated 582 stage I germ cell tumour (365 SGCTT and 208 NSGCTT including 111 combined S +NSGCTT). During this period, we routinely recommended adjuvant carboplatin (AUC7 based on EDTA clearance) for SGCTT, and adjuvant BEP x2 for VI+ NSGCTT after orchidectomy. VI− NSGCTT were offered both surveillance and adjuvant BEP x2. Seventy-two percent of VI− cases opted for ACT whilst 28% preferred surveillance. The outcomes are shown in Table 1. We have also published evidence showing that some patients would opt for ACT even at low levels (10%) of hypothetical recurrence risk, even some who have previously experienced BEP chemotherapy [42].

ongoing trials
German TC study group
The German TC study group has recently closed a randomised trial in high-risk stage 1 NSGCTT in which a control arm of BEP x2 was compared with an experimental arm of BEP x1. This trial opened in 2004 with a target accrual of 534 patients but failed to accrue adequately.

Table 1. Birmingham testicular tumour service 2000–2009

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Total</th>
<th>No. of recurrences</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma (ACT carboplatin x1)</td>
<td>356</td>
<td>9</td>
<td>2.5</td>
</tr>
<tr>
<td>NSGCTT+ combined</td>
<td>208</td>
<td>6</td>
<td>2.9</td>
</tr>
<tr>
<td>Adjuvant BEP x2 chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI+</td>
<td>71</td>
<td>1b</td>
<td>1.4</td>
</tr>
<tr>
<td>VI−</td>
<td>88</td>
<td>1b</td>
<td>1.1</td>
</tr>
<tr>
<td>Surveillance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI+</td>
<td>7</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td>VI−</td>
<td>34</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Recurrences in stage 1 testicular germ-cell tumours (TGCT).

*In eight cases pT stage (VI+ or VI−) or outcome not known. 

**One had suboptimal doses due to non-compliance and one had chemotherapy at another centre.

UK National Cancer Research Institute TC clinical study group
The UK National Cancer Research Institute TC clinical study group is conducting a single-arm study of one cycle of adjuvant BEP chemotherapy in high-risk (VI+) stage 1 NSGCTT (111 trial).

Ultimately, the point of clinical studies is to change practice. Despite there never having been a randomised trial of two cycles of adjuvant BEP versus surveillance (or RPLND), BEP x2 has been adopted in many countries across the world for high-risk stage 1 cases following the original MRC single-arm study supported by several smaller, confirmatory single-arm studies. Furthermore, a randomised trial of BEP versus surveillance would have recurrence risk as primary outcome and strict monitoring and stopping rules in the adjuvant arm would be required so that the trial could be stopped in the event of an unacceptably high recurrence rate emerging. Also the recurrence rate on surveillance has been remarkably consistent through multiple studies. In light of these facts, the arguments for a surveillance control arm become less persuasive.

In the light of this, a minimum sample size of 236 patients has been calculated. This will be sufficient to exclude a recurrence rate of 5%. The aim is to ensure that, if the recurrence-free rate is really 98% (i.e. as observed for BEP x2 in the original study [18], there is a high chance that the lower CI around the estimate of the recurrence rate is >95%. If 236 patients are entered and ≥229 are recurrence free, a recurrence-free rate >95% would be accepted. This design has a power of 80% and an alpha of 5%, i.e. there is an 80% chance that seven or fewer recurrences will be observed in 236 patients if the true recurrence rate is 2%, and a 5% chance that this will happen if the recurrence rate is 5%. Following extensive peer-review, the Cancer Research UK Clinical Trials Advisory Awards Committee has accepted the case for this single-arm study, and agreed to fund it. Currently (July 2012), 104 UK centres are collaborating and 83 cases have been accrued.

In summary, patients with stage 1 NSGCTT can be successfully managed either by a policy of surveillance with chemotherapy in the event of recurrence or by treatment with two cycles of ACT. Both the options result in the same excellent survival prospects but with different shortcomings. It may be the case, therefore, that there is no one single best...
treatment approach, rather an optimum plan for each individual. This emphasises the importance of offering clear information about different treatment options to patients accepting that some will wish their physician to decide.

management options for stage 1 SGCTT

A Europe-wide survey of management practices in stage 1 SGCTT was published earlier this year [43] demonstrating big differences in the patterns of care between specialties and countries. Seventy-one percent of 969 respondents were urologists, 15% medical oncologists, and 12% were radiation oncologists. Fifty-eight percent offered only one post-surgical option (18% only surveillance, 19% only radiotherapy and 21% only chemotherapy). Thirteen percent offered all three strategies, 25% surveillance and radiotherapy or chemotherapy, and 5% offered either adjuvant radiotherapy or chemotherapy without surveillance. In all 53% offered ACT. This is in contrast to a study from Canada published in 2006 in which only 1% of radiation oncologists offered ACT [44]. It is hardly surprising that the proportion of radiation oncologists offering chemotherapy is so low when the major trial which showed non-inferiority of a single dose of carboplatin [45] was conducted in Europe and was published in 2005, only a year before the Canadian survey was published.

adjuvant radiotherapy for stage 1 SGCTT

SGCTT are very radiosensitive and until recently radiotherapy had been the preferred adjuvant therapy for stage 1. With a low rate of relapse and manageable acute toxicity, it has been an attractive treatment option. Randomised, controlled trials have been carried out in an effort to minimise both dose and radiation volume [46–48]. As a consequence, the standard schedule of radiotherapy is now 20 Gy delivered in ten fractions to a para-aortic field. The main concern of this treatment modality is the possible induction of radiation-induced secondary cancers, and these concerns have grown steadily [49].

ACT for stage 1 SGCTT

As well as being extremely radiosensitive, seminoma is also very chemo-sensitive. In the early 1980s, Oliver et al. began to investigate first 2 then one cycle of adjuvant carboplatin [49, 50]. This work led to the MRC TE19/EORTC30982 trial of radiotherapy versus single-dose adjuvant carboplatin (AUC7) in 1447 patients with stage 1 seminoma [45]. With a median follow-up of 4 years it showed that carboplatin was non-inferior to radiotherapy. Patients given carboplatin were less lethargic and less likely to take time off work than those given radiotherapy, and there were preliminary data suggesting a reduction in new, second primary TGCT in the carboplatin radiotherapy, and there were preliminary data suggesting a reduction in new, second primary TGCT in the carboplatin.

In 2011, more mature results of this important trial were published. The relapse-free rates (RFR) at 5 years were 94.7% for carboplatin and 96.0% for radiotherapy (RT). Patients receiving at least 99% of the 7x AUC dose had a 5-year RFR of 96.1% (95% CI 93.4% to 97.7%) compared with 92.6% (95% CI 88.0% to 95.5%) in those who received lower doses (HR, 0.51; 95% CI, 0.24–1.07; P = 0.08). There was a clear reduction in the rate of contralateral GCTs (carboplatin, n = 2; RT, n = 15; HR, 0.22; 95% CI, 0.05–0.95; P = 0.03), and elevated pretreatment FSH levels (>12 IU/L) were a strong predictor of contralateral germ-cell tumour development (HR, 8.57; 95% CI, 1.82–40.38). Reassurance concerning potential late toxicity of single-dose carboplatin has been given in a recent publication documenting long-term follow-up (median, 9 years) in 199 patients in whom there was no increase in overall mortality or in death as a result of circulatory disease or the incidence of secondary, non-GCT malignancies [51].

surveillance for stage 1 SGCTT

Although existing evidence suggests that there is no serious long-term toxicity from a single cycle of adjuvant carboplatin, this is not conclusive since the numbers reported on long-term follow-up are relatively small. There are also worries about radiation exposure from frequent CT scans required on a surveillance programme. In view of this, a trial is running in the UK (TRISST) in which physicians enthusiastic about surveillance are offering their stage 1 seminoma patients randomisation in a non-inferiority trial of factorial design [52]. The four arms are: standard seven CT scans (6,12,18,24,36,48, and 60 months) versus three CT scans (6,18, and 36 months) versus seven MRI scans versus three MRI scans all over 5 years (56). The primary outcome is the number of cases in each arm relapsing with stage IIC (max diameter ≥5–10 cm) disease or worse. The trial aims to accrue 660 cases.

risk factors for recurrence in stage 1 SGCTT

In comparison with stage 1 NSGCTT (see below), the development of reliable, validated risk factors for recurrence in seminomas is lagging behind. In 2002, Warde et al. published a pooled analysis of the four largest studies of surveillance in stage 1 SGCTT including 638 cases in all [2]. With a median follow-up of 7.0 years (range 0.02–17.5 years), 121 relapses were observed for an actuarial 5-year RFR of 82.3%. On univariate analysis, tumour size (RFR: ≤4 cm, 87%; >4 cm, 76%; P = 0.003), rete testis invasion [RFR: 86% (absent) versus 77% (present), P = 0.003], and the presence of VI [RFR: 86% (absent) versus 77% (present), P = 0.038] were predictive of relapse. On multivariate analysis, tumor size (≤4 cm versus >4 cm, HR 2.0; 95% CI, 1.3–3.2) and invasion of the rete testis (HR 1.7; 95% CI, 1.1–2.6) remained as important predictors for relapse. Unfortunately, a recent attempt to validate this prospectively failed [53]. Consequently, we are currently unable to select management options reliably in stage 1 seminoma based upon recurrence risk.

disclosure

The authors have declared no conflicts of interest.

references


