Challenging the EAU 2009 Guidelines on Testis Cancer: The Risk-Adapted Management of Stage I Nonseminomatous Germ Cell Tumours: Surveillance Yields Equal Results With Less Toxicity

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Abstract

Introduction: One-third of patients with nonseminomatous germ cell tumour (NSGCT) present at clinical stage I (CS1), without evidence of metastatic disease on imaging and with normal postoperative tumour markers. The management of CS1 NSGCT following orchiectomy is controversial.

Methods: A Medline literature review was undertaken in December 2009. Management options include surveillance (with treatment for relapse), adjuvant cisplatin-based combination chemotherapy, or retroperitoneal lymph node dissection (RPLND).

Results: Only 30% of stage I NSGCT patients relapse during surveillance. Therefore, the 70% of patients who are cured by orchiectomy alone could be unnecessarily exposed to adjuvant treatment-related toxicity, including transient infertility, ototoxicity, possible development of second malignancy, and cardiovascular or neurologic symptoms. To reduce this overtreatment, the European Association of Urology (EAU) 2009 guidelines advise a “risk-adapted treatment approach,” recommending adjuvant two-cycle bleomycin, etoposide, and cisplatin (BEP) chemotherapy only for high-risk cases. Risk factors for relapse include the presence of vascular invasion (VI) by tumour cells in the primary tumour, which can help to predict relapse in 48% of patients, while 15% without VI and other risk factors eventually relapse. The reported 5-yr survival with surveillance and salvage treatment of relapse for men with non–risk-stratified CS1 NSGCT is 99%, while the risk-adapted 5-yr survival with adjuvant chemotherapy is >99%. The EAU guidelines propose two cycles of adjuvant chemotherapy (or RPLND) for those patients with VI, while those without VI are recommended to undergo surveillance. But this approach will result in 52% of patients receiving unnecessary treatment, while a few under surveillance will still relapse.

Conclusion: Based on minimising toxicity and excellent published outcomes, it is proposed that all CS1 NSGCT patients be managed by careful surveillance with salvage treatment only for relapse. Another option may be to give high-risk patients a single cycle of BEP to reduce toxicity.
1. **Introduction**

Primary testicular cancer is the most common malignancy in men aged 25–40 yr; in the United Kingdom, 2109 cases were diagnosed (2005), and approximately 90 men die every year. The incidence is increasing, affecting 6–10 per 100 000 men in Europe. Of these cases, 90% are germ cell tumours, of which 42% are nonseminomatous germ cell tumour (NSGCT). Following radical orchiectomy, 33–50% of NSGCTs are clinical stage I (CS1), which is defined as TxN0M0 according to postoperative serum markers and computed tomography (CT) scanning. Of all CS1 NSGCT patients, 70% are cured by surgery alone. However, 30% of these patients harbour occult metastatic disease, mostly in the retroperitoneum, and will relapse [1,2].

The management of CS1 NSGCT following orchiectomy is controversial. Options include surveillance (with salvage treatment for relapse), adjuvant cisplatin-based combination chemotherapy, or retroperitoneal lymph node dissection (RPLND). Because only 30% of patients relapse during surveillance, 70% of patients who are cured by orchiectomy alone could be unnecessarily exposed to adjuvant treatment-related toxicity. To reduce this overtreatment, the European Association of Urology (EAU) 2009 guidelines advise a “risk-adapted treatment approach,” recommending adjuvant treatment only for high-risk cases [3].

2. **Risk-adapted adjuvant treatment for clinical stage I nonseminomatous germ cell tumours**

2.1. **Risk factors for relapse**

Risk factors for relapse include the presence of vascular invasion (VI) by tumour cells in the primary tumour, which can help to predict relapse in 48% of patients. Therefore, 52% of VI-positive patients will not relapse, and 15% of patients without VI and other risk factors will relapse. Other risk factors in the primary tumour include lymphatic invasion, embryonal carcinoma (EC), the absence of yolk sac tumour, and positive MIB-1 staining. At best, using these factors, a combination of VI positivity plus >70% MIB-1 staining plus >50% EC predicts relapse in 64% of patients [4]. The EAU 2009 guidelines favour the use of VI as the best risk factor for relapse. The guidelines propose two cycles of adjuvant combination chemotherapy—bleomycin, etoposide, and cisplatin (BEP)—or RPLND are offered to those high-risk patients with pT2 (VI-positive) N0M0 or pT3–4N0M0, while those low-risk cases (pT1N0M0, without VI) are recommended to undergo surveillance [3]. However, this strategy will still result in 52% of patients receiving unnecessary treatment, while 15% of patients under surveillance will still relapse.

2.2. **Outcomes of adjuvant chemotherapy**

It should be clarified that no level 1 evidence of benefit exists for the use of adjuvant chemotherapy in this clinical setting. Given two cycles of BEP, only 3% of patients relapse; therefore, the risk reduction for relapse is 90%. Long term, >99% of patients are cured [5]. The risk-adapted 5-yr survival with adjuvant chemotherapy is without doubt excellent, at 99% [6]. A recent study using just one cycle of BEP demonstrated just 3.2% of patients relapse, so the risk reduction for relapse is 88% [7]. The benefit in terms of reduction in toxicity by giving only one instead of two cycles of BEP has yet to be determined.

2.3. **Toxicity of bleomycin, etoposide, cisplatin chemotherapy**

The toxicity of BEP chemotherapy has been well documented, mostly with reference to the usual salvage treatment dose of three cycles. Toxic effects include hair loss and neuropaenia in most cases; transient infertility is likely, and cryopreservation is necessary; a 2–7 times increased risk of cardiovascular effects, including hypertension. Reynaud’s phenomenon, myocardial ischaemia or infarction, and cerebrovascular accident up to 15 yr later [8,9]; renal impairment in 20–30% of patients, mostly subclinical [10]; anxiety, depression, and weight gain [11]; too-toxicity in 23–30% of patients [12]; neuropathy in 30% of patients [12]; and finally, an estimated 1.5 times risk of second primary cancer development [13].

3. **Surveillance for clinical stage I nonseminomatous germ cell tumours**

**Surveillance** is the process of monitoring the behaviour of disease in order to minimise overtreatment while detecting and treating early relapse. Various regimes of serial clinical examinations, serological tumour markers, and CT imaging (chest, abdomen, and pelvis) have been described. Because 88% of relapses occur during years 1 and 2 postorchiectomy, while relapses are rarely reported after >5 yr follow-up, surveillance tends to be more intensive during the first 2 yr and decreases beyond 5 yr.

3.1. **Non-risk-adapted surveillance**

Two groups have recently reported excellent results. In Toronto, 371 patients were managed by surveillance between 1981 and 2005. Overall, as expected, 28% of these patients relapsed, which included 52% of the high-risk VI-positive patients and 16% of the low-risk VI-negative patients. Five-year disease-specific survival (DSS; following salvage BEP with or without RPLND) was almost 100%, with just three (<1%) deaths [14]. The British Columbia group described surveillance of 223 patients, with a median follow-up of 52 mo. Of note, only 27% of patients exhibited VI. Overall, 26% or patients relapsed, including 51% VI-positive patients and—surprisingly—at least 37% of VI-negative patients. The authors reported that 74% of patients were spared any further treatment, while DSS was 100% [15].

A potential pitfall with surveillance is poor patient compliance, which could result in late presentation of advanced disease less amenable to curative salvage treatment. However, there is no evidence that this is the case; indeed, at least three studies (cited in Ref. [14]) have
demonstrated no difference in relapse rates between compliant and noncompliant patients.

4. Conclusions

There is no level 1 evidence to support the risk-adapted adjuvant treatment approach advocated in the EAU 2009 guidelines for CS1 NSGCT patients. Indeed, by comparison of cancer outcomes, surveillance appears as effective but avoids unnecessary treatment toxicity for half of the patients deemed at high risk for relapse (but will not do so). If the toxicity of only one cycle of BEP were demonstrated in a randomised trial to be significantly lower than that of two cycles but with equal efficacy, then the recommendations in the EAU guidelines could be modified accordingly; and if not, why should surveillance not be recommended for all CS1 NSGCT patients?

Conflicts of interest

The author has nothing to disclose.

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References