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Editorial Comment

'Active surveillance' for stage I testis cancer: attaining maturity at 21 years

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Just 21 years ago, Michael Peckham, a former Editor in Chief of the *European Journal of Cancer*, and then Professor and Chair of the Department of Academic Radiotherapy at the Royal Marsden Hospital, led his group in beginning an innovative study that addressed the important issue of whether radiotherapy could safely be omitted from the routine management of stage I non-seminomatous germ cell tumours (NSGCT). Their preliminary data suggested that a policy of close observation after orchiectomy for stage I NSGCT gave comparable cure rates to contemporary series of retroperitoneal lymph node dissection (RPLND), and that further investigations were indicated [1].

Building on the important early observations from Tom Sandeman and colleagues in Australia [2], the group at the Royal Marsden Hospital studied prognostic factors in stage I disease, identifying adverse prognostic determinants that might lead to an increased risk of relapse in surveillance protocols [3]. At that time it was clear that advanced T-stage and slow clearance rates of circulating tumour markers were associated with a significantly increased risk of relapse [3], and that vascular invasion was probably an adverse prognosticator. These data were confirmed in North American series [4,5], reflecting experiences at the University of Minnesota and at the Memorial Sloan Kettering Cancer Center. These important observations were codified by the major study of the British Medical Research Council, which identified embryonal carcinoma and advanced T-stage as independent adverse prognostic determinants, and the presence of endodermal sinus tumour elements as a favourable determinant of outcome [6].

The safety of omitting radiotherapy from the management of stage I NSGCT was demonstrated effectively by the randomised trial of the Danish Testicular Cancer Group [7]. In this important trial, radiotherapy reduced the risk of abdominal nodal relapse, but did not improve overall survival. Antedating these studies, and continuing to the present time, retroperitoneal lymph node dissection has remained one of the standards of care. To this day, one of the particular benefits of the lymph node dissection is the reduction of the risk of intra-abdominal relapse, with a concomitant reduction of the chance of requiring chemotherapy [8].

In the past two decades, several groups have documented experience in the policy of active surveillance, culminating in the important report in this issue of the *European Journal of Cancer* pp. 1925–1932. There is a consensus that the policy of active surveillance is a reasonable alternative to RPLND, and that adjuvant radiotherapy no longer has a role in the management of stage I NSGCT. Policies of retroperitoneal lymph node dissection or active surveillance produce cure rates higher than 95% in centres of excellence [9].

However, for many years, the optimal approach to active surveillance, with respect to the frequency of follow-up and the protocol for testing at each visit had not been defined [10]. Specific unresolved issues included the frequency of follow-up visits, necessity for monthly or second monthly computed tomography (CT) scans, and the late hazards of this approach. However, the investigators from Charing Cross Hospital have indicated that it is probably safe to reduce the frequency and intensity of CT scanning protocols, provided that patients are followed clinically and by meticulous serial marker measurement. It should not be assumed that these excellent results necessarily translate to the setting of routine clinical practice. The Charing Cross Hospital has a long and distinguished record of well structured clinical trials in germ cell tumours, and have paid careful attention to the execution of their protocols, including the details of follow-up. In an unstructured clinical environment, it is very easy to lose track of patients, and

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a recall system should be in place whenever possible to avoid this problem.

The basis of using active surveillance is completely predicated on the efficacy of chemotherapy for patients with 'good risk' or limited-extent metastatic disease. For patients with small volume pulmonary metastases and tumour marker levels less than 1000 ng/ml, the chance of cure with chemotherapy is greater than 90% in centres of excellence [11–14]. However, this requires due diligence to the administration of chemotherapy, absence of inappropriate or random reduction or alteration of drugs and doses, and careful adherence to protocols of follow-up. A common practice in recent years has been the attempt to reduce the toxicity of treatment via the modification of standard protocols of chemotherapy. However, it has now clearly been shown that deletion of bleomycin [15,16] or replacement of cisplatin by carboplatin [17] for the treatment of advanced NSGCT leads to inferior survival figures. When incorporated into salvage treatment after failure of active surveillance, these modifications are potentially disastrous.

The optimal management of NSGCT that relapse only in abdominal lymph nodes after active surveillance is controversial. There is general agreement that radiotherapy has no role. However, there are proponents of retroperitoneal lymph node dissection who view the standard surgical approach as offering both diagnosis and definitive treatment, citing surgical cure rates of 50% or more, particularly in patients with only microscopic evidence of lymph node involvement [18]. It is not yet clear that the use of lymph node dissection alone as definitive treatment for apparent relapse after a prolonged period of active surveillance is completely safe. In this situation, the chance of dissemination beyond the retroperitoneum is probably increased due to the delay occasioned by the period of surveillance. In this situation, delay of chemotherapy could theoretically increase the risk of treatment failure. The alternative approach is to offer first-line cytotoxic chemotherapy to such patients, based on cure rates approaching 100% for patients with small volume metastases that are limited to the retroperitoneal nodes. The attraction of this approach is that it reduces the morbidity from surgery and the risk of extra-abdominal relapse, but this may be offset by the acute toxicity of chemotherapy and the potential for late complications. To date, no randomised trial has attempted to resolve this issue, and the decision is usually predicated on the biases of the clinician and the preferences of the patient.

Williams and colleagues [19] addressed the issue to some extent in the context of initial treatment (without a period of active surveillance). They studied 195 patients with stage II NSGCT who were randomly allocated to receive two cycles of adjuvant chemotherapy or to undergo a programme of observation with salvage chemotherapy at the time of relapse. However, this group of patients included cases with extensive (> 5 cm) retroperitoneal lymph node disease. Nearly 50% of the observation-only cases relapsed, although the majority were salvaged with chemotherapy. An equivalent proportion of patients treated with adjuvant chemotherapy survived, and it was concluded that there was no statistically significant difference in outcome.

Another controversial issue is the management of the patient with marker-only disease (i.e. without evidence of specific lymph node or other metastases, but with elevation of serum marker levels at relapse). RPLND will identify occult lymphatic involvement in some cases treated at initial presentation, achieving cure in up to half of them. Nevertheless, up to 50% of the patients undergoing surgery will eventually require chemotherapy, and it is not clear whether a greater proportion will require chemotherapy after surgery for relapse after active surveillance. In this situation, the cure rates with cytotoxic chemotherapy are close to 100%, although there is a risk of additional late toxicity as compared with surgery alone. In the situation of the relapsing patient with marker-only disease, my own practice has been to use initial combination chemotherapy, reserving surgery for the occasional patient in whom persistent lymph node enlargement is subsequently identified on CT scan. Of course, the presence of a contralateral second primary testicular tumour must be excluded first.

For patients who relapse with lymph node metastases measuring more than 5 cm in diameter (stage IIC or stage C disease) and for those with visceral metastases (lung, liver, bone, etc.), the treatment of choice is systemic chemotherapy [11–14].

In the past few years, based on the identification of adverse prognostic factors for stage A (I) disease, several groups have advocated the use of initial adjuvant chemotherapy for patients with advanced T-stage or other adverse factors [20–22]. While preliminary results have been interesting, I would encourage a greater level of caution before this approach is viewed as a standard of care, especially as it has not been effectively tested in a randomised clinical trial. While early control of occult disseminated cancer is clearly desirable, the potential costs of late toxicity should not be forgotten.

A detailed review of the toxicity of treatment is beyond the scope of this editorial, and has been covered in detail elsewhere [23,24]. The acute toxicity of chemotherapy has been well defined, and includes the potential for nausea and vomiting, myelosuppression, alopecia, allergic phenomena, pneumonitis, infection, anorexia and a range of relatively uncommon complications. Most of these can be controlled by modern supportive techniques. The chronic or delayed side-effects of treatment are now becoming increasingly recognised (Table 1), especially as the medical community has become used to the concept of germ cell tumours as a curable entity and the focus is now shifting to the avoidable

costs of such cure. In surveys of patients surviving 5–10 years after chemotherapy for testicular cancer, the frequency of serious late toxicity is relatively low [25]. Nevertheless, a high level of subtle biochemical, neurological, renal and vascular toxicities has been identified [25]. In particular, cerebrovascular and cardiovascular complications [26], hypertension, Raynaud's phenomenon [27] and hypercholesterolaemia [28] have been identified in cohorts of cured patients that have not yet reached the classical age for the presentation of cardiovascular and cerebrovascular diseases. It is thus quite possible that incidence figures for these complications will rise as these patients age. Similarly, the demonstration of increased potential risks of second malignancies, including leukaemia [29], sarcoma and melanoma [30] is of concern, and should be factored into programmes that advocate routine use of adjuvant chemotherapy for high-risk stage I disease. The continuation of careful and focused follow-up will be essential for these patients, despite the efforts of many health insurance organisations to reduce structured specialist follow-up by returning the care of these patients to their family practitioners.

A sense of perspective must be maintained. Testicular cancer was formerly a relentless killer of young males, and one must recognise that tremendous progress has been made in only 20 years. One should not make the mistake of modifying or delaying effective treatment to avoid the small risk of late complications. Instead, the logical approach is to offer curative therapy for patients with a curable cancer, and then to follow the patients in a structured fashion, allowing appropriate diagnosis and early management of any complications that ensue.

Table 1
Late effects of chemotherapy for germ cell tumours [31]

Organ system/or problem	Potential toxicity
Cardiovascular	Hypertension
	Coronary artery disease
	Peripheral vascular disease
	Cerebrovascular disease
	Raynaud's phenomenon
	Hyperlipidaemia
Neurological	Peripheral neuropathy
	Autonomic neuropathy
	Hearing loss
Psychosocial	Marital problems
	Infertility
	Employment problems
	Legal/sociopathic
Pulmonary	Pneumonitis/fibrosis
renal	Renal failure/nephritis
	Hypomagnesaemia
	Hyperuricaemia
Second malignancies	Leukaemia/solid tumours

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