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European Journal of Cancer 36 (2000) 1925–1932

European Journal of Cancer

www.ejconline.com

Surveillance for stage I testicular germ cell tumours: results and cost benefit analysis of management options

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Received 6 October 1999; received in revised form 7 January 2000; accepted 10 May 2000

Abstract

Between 1979 and 1996 303 men with stage I testicular germ cell tumours (120 seminoma and 183 non-seminomatous germ cell tumours (NSGCT)) were enrolled onto a programme of surveillance. In our institutions the frequency of computed tomography (CT) scans is reduced compared with other centres. For all 303 men, the median follow-up is 5.1 years (range: 0.1–21.7 years) and there have only been 3 deaths (1 from disease, 1 from neutropenic sepsis and 1 from secondary leukaemia). 52/183 (28%) patients with NSGCT and 18/120 (15%) patients with seminoma have relapsed. The relapse-free survival at 5 years is 82% for seminoma and 69% for NSGCT (Logrank $P=0.004$). All men who relapsed, except 1 man with NSGCT, were in the International Germ Cell Cancer Collaborative Group good or intermediate prognosis group at relapse. Half of the seminoma relapses presented with symptoms and 31% of the NSGCT relapses. The remaining relapses were detected serologically or radiologically by the surveillance programme. 5 men (2%) on surveillance, 3 with initial diagnosis of seminoma and 2 with NSGCT, have developed second contralateral testis tumours (all stage I seminomas). In a well motivated centre a policy of surveillance for stage I testicular germ cell tumours (both NSGCT and seminoma) is associated with a low mortality rate (3/303, 1%) and may have the advantage of sparing overtreatment with potentially toxic therapies in this group of young men.

Keywords: Testicular, germ cell; Tumours; Stage I; Surveillance

1. Introduction

Testicular germ cell tumours represent approximately 1% of all male tumours. They are, however, the commonest malignancy in men aged 15–35 years, and are, in the majority of cases, curable. The management of stage I testicular germ cell tumours varies considerably across Europe and the USA and includes surveillance, retroperitoneal lymph node dissection (RPLND), adjuvant chemotherapy and for seminoma, adjuvant radiotherapy. This variation reflects uncertainty as to which management strategy provides the best cost to benefit ratio. The least invasive option is surveillance but as this involves frequent clinic visits, serial tumour marker estimations and radiological investigations it requires motivation on behalf of both patient and physician. There is good evidence that frequent tumour marker estimations may help to detect relapses early, thus placing patients in a better prognostic group [1]. In contrast, less is known about how frequently patients should be reviewed in clinic or radiological investigations performed. The frequency of interventions should be such that the positive predictive value of the investigation is maximal and interval relapses are minimal.

In this paper we have analysed our experience of surveillance for both stage I non-seminomatous germ cell tumours (NSGCT) and seminomas.

2. Patients and methods

Between 1979 and 1996 332 men with stage I testicular germ cell tumours were referred following orchidectomy. Complete staging investigations were undertaken within

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0959-8049/00/$ - see front matter
PII: S0959-8049(00)00140-4

a month of orchidectomy including whole body computed tomography (CT) scans and measurement of the serological tumour markers, alpha fetoprotein (AFP), human chorionic gonadotrophin (hCG) and lactate dehydrogenase (LDH). If there was no clinical or radiological evidence of metastasis and the tumour markers had returned to within the normal range, patients were offered enrolment into a surveillance programme. In total, 303 patients (183 NSGCT and 120 seminomas) were enrolled into this programme. Overall during this time, 195 men were referred with stage I NSGCT and 183 (94%) opted for surveillance the remaining 12 receiving adjuvant chemotherapy and 137 men with stage I seminoma were referred of whom 120 (88%) opted for surveillance whilst 17 men received adjuvant irradiation. The surveillance programmes which have been in place since 1979 for NSGCT and seminoma are outlined in Table 1. Men with NSGCT have CT scans at 3 and 12 months postorchidectomy only. Men with seminoma have CT scans 3, 6, 12 and 24 months postorchidectomy only.

2.1. Statistical methods

Survival was calculated from the day of diagnosis until death or the date of last follow-up. Overall survival duration curves were plotted according to the method of Kaplan and Meier [2]. The log-rank method was used to test for the significance of differences in survival distributions [3].

3. Results

3.1. NSGCT surveillance programme

The median follow-up for the surveillance cohort of 183 patients is 5.8 years (range: 0.1–21.7 years).

3.1.1. Survival

The overall survival at 5 years is 100% and at 10 years is 98.9% (95% confidence interval (CI) 96–100). There have only been 2 deaths (1%) in this cohort of men.

3.1.2. Relapse

52 patients (28%) have relapsed after enrolment into the surveillance programme. The overall relapse-free survival at 5 years is 69% (95% CI: 61–76) (Fig. 1).

3.1.3. Detection of relapse

The initial presentation of relapse was symptomatic in 16 NSGCT patients (31%), while the remaining 36 patients were diagnosed by radiological (12), serological (21) or combined (3) investigations (Fig. 2). Following presentation or suspicion of relapse staging was completed and 30 men had elevated tumour markers and 26 had radiological abnormalities. The median time to relapse for the NSGCT surveillance cohort was 6 months (range: 1 month–10.2 years). As expected most of the NSGCT patients who relapsed had raised serum tumour markers (58%) or radiological abnormalities at relapse (50%) while only 31% had symptoms.

Table 1
Surveillance programme[a]

		NSGCT	Seminoma
1st year	Clinic visit	Monthly	Monthly
	Tumour markers	2 Weekly (0–6 months)	2 Weekly (0–6 months)
		Monthly (6–12 months)	Monthly (6–12 months)
	CXR	Monthly	Monthly
	CT scan	+3 Months	+3 Months
	(abdominal/thorax)		+6 Months
		+12 Months	+12 Months
2nd year	Clinic visit	2 Monthly	2 Monthly
	Tumour markers	Monthly	Monthly
	CXR	2 Monthly	2 Monthly
	CT scan		+24 months
	(abdominal/thorax)		
3rd year	Clinic visit	3 Monthly	3 Monthly
	Tumour markers	2 Monthly	2 Monthly
	CXR	3 Monthly	3 Monthly
4th and 5th year	Clinic visit	4 Monthly	4 Monthly
	Tumour markers	3 Monthly	3 Monthly
	CXR	4 Monthly	4 Monthly
6th year onwards	Clinic visit	6 Monthly	6 Monthly
	Tumour markers	6 Monthly	6 Monthly
	CXR	6 Monthly	6 Monthly

CXR, Chest X-ray; CT, computerised tomography; NSGCT, non-seminomatous germ cell tumours.

[a] The serum tumour markers measured were hCG (human chorionic gonadotrophin), AFP (alpha fetoprotein) and LDH (lactate dehydrogenase). CXR are not performed the same month as CT scans.

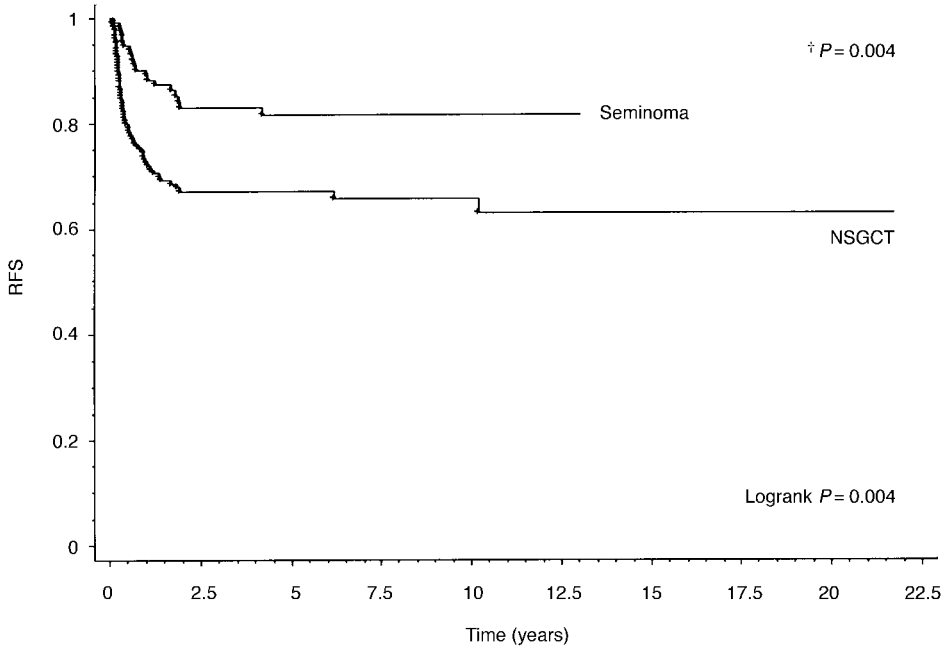

Fig. 1. Kaplan–Meier relapse-free survival (RFS) by histological classification.

3.1.4. Sites of relapse

At relapse, 14 NSGCT patients (27%) had stage IM disease with no radiological abnormalities but elevated tumour markers. 24 patients (46%) had para-aortic lymphadenopathy as the sole site of relapse, 9 (17%) had only pulmonary metastases at relapse and 2 men (4%) with NSGCT had local recurrence only (1 scrotal, 1 inguinal). 2 patients (4%) had mediastinal disease as the only site of relapse and one (2%) had extensive disease at relapse including liver, lung and para-aortic disease (Table 2). All, except the latter patient, were in the International Germ Cell Cancer Collaborative Group (IGCCCG) good or intermediate prognosis group at relapse [4].

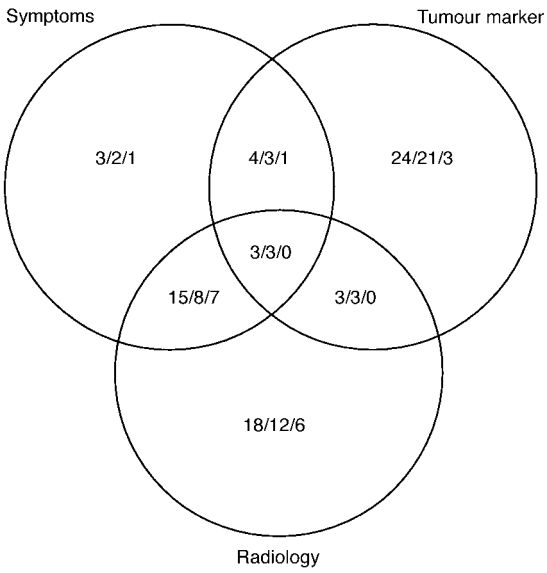

Fig. 2. Venn diagram illustrating the features at relapse presentation according to the presence of symptoms raised tumour markers or radiological abnormalities at relapse. In each sector, the numbers refer to the total number of relapses/number of NSGCT relapses/number of seminoma relapses that fall within the criteria.

3.1.5. Deaths

2 patients with NSGCT have died in this cohort. One patient with teratoma relapsed 6 years after orchidectomy and died of neutropenic sepsis during chemotherapy in the pre-colony stimulating factor era. The second patient who had a mixed GCT and relapsed in the mediastinum 17 months after orchidectomy was treated with cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide (POMB/ACE) combination chemotherapy. He died of acute myelomonocytic (FAB subtype M4) leukaemia 26 months after completing POMB/ACE chemotherapy having received a total cumulative etoposide dosage of 900 mg/m^2. Karyotype analysis of the leukaemic clone

Table 2
Sites of relapse

	All (*n*)	%	NSGCT	%	Seminoma	%
Stage IM	15	21	14	27	1	6
Para-aortics only	41	59	24	46	17	94
Lung only	9	13	9	17	0	
Local only	2	3	2	4	0	
Mediastinum only	2	3	2	4	0	
Extensive	1	1	1	2	0	
Totals	70	100	52	100	18	100

NSGCT, non-seminomatous germ cell tumours.

demonstrated the presence of the t(8;21)(q22;q22) chromosomal translocation.

3.2. Seminoma surveillance programme

The median follow-up for the seminoma surveillance cohort of 120 patients is 4.6 years (range: 0.1–19.0 years).

3.3.1. Survival

The overall survival at 5 years is 100% and at 10 years is 94.4% (95% CI 86–100). There has only been one death in this cohort of men.

3.3.2. Relapse

18 patients (15%) with seminoma have relapsed after enrolment into the surveillance programme. The overall relapse-free survival at 5 years is 82.0% (95% CI: 74–90) (Fig. 1).

3.3.3. Detection of relapse

The initial presentation of relapse was symptomatic in 9 patients (50%), whilst the remaining 9 patients were diagnosed by radiological (6) or serological (3) investigations (Fig. 2). Following presentation or suspicion of relapse staging was completed and 4 men had elevated tumour markers and 13 had radiological abnormalities. The median time to relapse for the seminoma surveillance cohort was 4 months (range: 1 month–4.2 years). Most of those patients with seminoma who relapsed had radiological abnormalities (72%) although 50% had symptoms and only 22% raised markers at relapse.

3.3.4. Sites of relapse

None of the patients with seminoma relapsed with disease beyond the para-aortic lymph nodes 17 (94%) relapsed in the para-aortic lymph nodes and 1 patient (6%) had stage IM with no radiological site of disease (Table 2).

3.3.5. Deaths

One patient in the seminoma cohort died, despite chemotherapy, radiotherapy and high-dose chemotherapy with stem cell transplantation, from chronic relapsing seminoma following a relapse detected 21 months after orchidectomy.

3.3.6. Second primary tumours

Of the total of 332 men with stage I testicular GCT, 7 (2%) developed second primary contralateral tumours. 5 men were enrolled on the surveillance programme, 1 man had received radiotherapy for stage I seminoma and 1 had been treated with adjuvant chemotherapy for stage I seminoma. The initial diagnosis was seminoma in 5 patients and teratoma in 2 patients and the second primary tumour was a stage I seminoma in all 7 cases. The median interval between diagnosis of the first and the second tumours was 6 years (range: 3–8 years). In addition, 1 man on the surveillance programme developed a second primary superficial bladder tumour.

3.3.7. Late relapses

In total 3 men have relapsed more than 2 years after the orchidectomy. One man with stage I seminoma relapsed after 4.2 years with symptomatic para-aortic adenopathy and elevated tumour markers. He was treated successfully with chemotherapy and radiotherapy and remains in remission 4 years later. One man with a mixed GCT including teratoma, embryonal carcinoma and seminoma relapsed after 6.2 years. He was treated with chemotherapy but died of neutropenic sepsis (*vide supra*). A third man with teratoma including yolk sac and embryonal carcinoma elements relapsed after 10.2 years. He was treated with chemotherapy and remains in remission 3 years later.

4. Discussion

Stage I testicular germ cell tumours have an excellent prognosis. The current favoured treatment options all give very similar rates of long-term survival in the order of 98% over a 5–10-year period.

Stage I NSGCT is currently managed either by surveillance, with less than 30% of patients expected to relapse and require salvage treatment with combination chemotherapy, or by nerve-sparing RPLND. The argument against subjecting all clinical stage I NSGCT patients to nerve sparing RPLND is that only 10–25% [5] of patients at surgery have disease in their retroperitoneal lymph nodes so 75–90% undergo an invasive procedure for no immediately apparent benefit. Nerve-sparing RPLND does not guarantee that a patient will not relapse, and the rates of conservation of fertility are dependent upon the skill and experience of the surgeon. There is no doubt that at experienced centres the infertility rate is very low, however, this is not a standardised finding. Patients following RPLND still require further follow-up surveillance for relapse.

A surveillance policy is ideally suited to stage I NSGCT because most tumours produce serological tumour markers and the majority of relapses occur within the first 2 years after orchidectomy. The most frequent sites of relapse are the retroperitoneal lymph nodes or lungs. This was reflected in our study with 46% of NSGCT relapses in the para-aortic lymph nodes and 17% in the lungs while 27% only had raised serum markers with no apparent site of disease. A surveillance policy does, however, require a high level of physician and patient motivation, as non-attenders risk presenting late with large volume and difficult to salvage disease. In our study only a single patient presented at relapse with

poor prognosis disease (IGCCCG poor prognosis group). In our surveillance programme the tumour marker estimations initially were performed at fortnightly intervals which is more frequently than in other protocols [6,7] and was supported by an analysis of serum tumour marker doubling rates [1]. However, the radiological investigations were performed less frequently than in other centres. Our results of a relapse rate of 31% for NSGCT with surveillance over 5 years is comparable with other studies. The optimal timing of screening investigations in surveillance programmes does, however, remain uncertain.

The identification of a subgroup of patients with stage I NSGCT with lymphovascular invasion at high risk of relapse has led to recent trials of two courses of adjuvant BEP (bleomycin, etoposide and cisplatin) chemotherapy in the hope of reducing recurrence. The early evidence shows that this does appear effective and may reduce the rate of recurrence from 40–50% down to 5–8% [8–10]. However, salvage treatment may be more difficult in those who recur because of the development of chemoresistance. The salvage rates in the current studies are variable and it is too early to interpret the data on account of the very small numbers. There is again the problem of overtreating 50% of patients with chemotherapy, for which we are not yet fully aware of the long-term toxicities, including the effect on fertility, the risk of chemotherapy-induced second tumours and increased vascular disease [11]. There is also significant histopathological variability in reporting of lymphovascular invasion.

The current accepted treatment options for stage I seminoma include irradiation to the para-aortic lymph nodes and surveillance. Seminoma is very radiosensitive and tends to relapse in a predictable pattern, with the para-aortic lymph nodes as first site of relapse. Radiotherapy to the para-aortic lymph nodes is associated with very low recurrence rates (2–5%) and an extremely high rate of disease-related cure. However, there are significant radiotherapy-associated morbidities including peptic ulceration and bowel disturbances [12]. There is also an increasing concern over the apparent 2–3-fold increase in the risk of developing a second cancer, including stomach cancer and sarcomas [13]. In our small series at the Charing Cross Hospital, London, of 17 patients treated with irradiation there was 1 relapse (6%) which occurred 8 months after treatment.

Surveillance has shown that only approximately 18% of men with stage I seminoma will relapse, so with adjuvant radiotherapy over 80% are being given potentially toxic treatment without benefit. Surveillance, however, in stage I seminoma is associated with problems as only 10–20% are marker positive and there are occasional late relapses, so long-term follow-up is required. In our series, 15% of stage I seminomas relapsed. Almost all relapsed in the retroperitoneal lymph nodes (94%) with only 1 (6%) patient relapsing with elevated serum tumour markers. One patient relapsed 4.2 years after orchidectomy and all 18 patients who relapsed were in the IGCCCG good prognosis group at relapse. Salvage treatment is usually very effective and a surveillance policy is associated with very high long-term survival in motivated centres.

There has been at least one pilot study of adjuvant chemotherapy with one or two courses of carboplatin in stage I seminoma [14]. This showed a relapse-free survival rate at 5 years of 99% which was comparable with those treated with radiotherapy and surveillance [14]. However, more information on the long-term effects of even short courses of chemotherapy need to be obtained.

Morbidity is very difficult to quantify for the treatment options in stage I testicular GCT. Infertility is an important issue in this group of generally young men. It is recognised that men with testicular tumours tend to be subfertile at diagnosis. Approximately 40–50% are oligospermic prior to any treatment [5]. Sperm storage should be offered to all men, where possible, prior to treatment with combination chemotherapy because of the potential for long-term infertility. It is recognised that over half the men will have subnormal sperm counts at diagnosis and combination chemotherapy produces infertility rates of approximately 50% after 12 months, falling to 20–25% after 2–3 years [12]. However, only half the men who attempt fatherhood after chemotherapy will succeed [15,16] and this rate may be increased by assisted fertilisation using pretreatment cryopreserved sperm [17]. The impact of adjuvant chemotherapy on infertility has not yet been adequately established, although it does not appear as high as three or more courses of salvage combination chemotherapy [9]. The psychological impact of surveillance has been raised, however, it is difficult to accurately ascertain, and all forms of currently recommended treatment entail some surveillance in order to detect recurrences early. No formal prospective psychological evaluation has been undertaken as yet to compare adjuvant treatment with surveillance. Clearly some patients will be anxious whilst on a surveillance programme because of the higher chance of relapse and more frequent hospital visits. Other patients prefer the opportunity to avoid the short- and long-term toxicities of surgery, chemotherapy or radiotherapy. In one study where no patients on a surveillance programme had reduced semen volumes, sexual dysfunction rates were similar in patients on the surveillance programme, following RPLND, and following adjuvant chemotherapy or radiotherapy [18].

A surveillance policy in both stage I seminoma and NSGCT is highly effective in a motivated centre, providing 98–99% long-term survival with minimal morbidity and good cost-effectiveness. It has the advantage

of only treating those patients who relapse and sparing overtreatment with potentially toxic adjuvant surgery, chemotherapy or radiotherapy.

Appendix A

Cost-benefit analysis

A cost-benefit analysis was performed comparing this surveillance policy in stage I testicular germ cell tumours with the other management options of nerve sparing retroperitoneal lymph node dissection (RPLND), adjuvant chemotherapy or irradiation (seminoma only). The factors for comparison were mortality rates and cost over a 10-year period. These were extrapolated as predicted values per 1000 males with stage I testicular GCT.

Mortality

Surveillance

Several studies have shown that a policy of surveillance is associated with an approximately 98.4% long-term survival (16 deaths/1000) [19,20]. Although there is a 25% relapse rate over 10 years, the salvage rate with combination chemotherapy is approximately 95%. Deaths occur either because of a failure to respond to chemotherapy (12/1000; 1.2%) or because of treatment-induced toxicity such as neutropenic sepsis or second cancers (4/1000; 0.4%).

RPLND

Nerve sparing RPLND similarly has an overall survival of 98% (20 deaths/1000) [19,21]. Approximately 17% of clinical stage I (7% of pathological stage I and 30% of pathological stage II) will relapse over 10 years (170 relapses/1000) [5,22] with a salvage rate from chemotherapy of 90%. Deaths occur because of operative complications (1/1000; 0.1%), failure to respond to treatment (17/1000; 1.7%) or chemotherapy-related short- and long-term complications (2/1000; 0.2%).

Adjuvant chemotherapy

Adjuvant chemotherapy using two courses of BEP chemotherapy has recently been advocated in patients with stage I NSGCT thought to be at high risk of relapse due to lymphovascular invasion. This group of patients has been shown to have a 40–50% risk of relapse if managed by surveillance alone [9]. The studies to date have used small numbers and are not yet subject to long-term follow-up. However, the overall survival appears to be approximately 98% (22 deaths/1000) [9,10]. The relapse rate is approximately 5–11% [8–10] with a salvage rate from 50 to 90% [10]. The deaths will be from treatment resistance (20/1000) or chemotherapy-related deaths — the majority of these from the salvage rather than the adjuvant therapy (2 deaths/1000).

Adjuvant radiotherapy

Radiotherapy is often used in stage I seminoma. The overall survival is approximately 98.5% (15 deaths/1000) [23–25]. The relapse rate is 4–6% [26–28] with a salvage rate with combination chemotherapy of 90%. Deaths are from disease resistance (5/1000) or treatment-related deaths including deaths from radiation-induced second cancer (10/1000) [13,29].

Cost

Surveillance

Table A1 summarises the cost of the surveillance programme at Charing Cross Hospital. It costs £4900 per seminoma patient and £4612 per NSGCT patient for 10 years surveillance for stage I tumours. Twenty five per cent of patients relapse and require combination chemotherapy. Table A2 shows the cost of POMB/ACE chemotherapy for relapse is £4549.19 per patient which in subsequent calculations is rounded up to £4550 for convenience. Fifteen per cent of those who relapse and require combination chemotherapy will also require surgical resection of residual masses (usually retroperitoneal) which costs £3600 per patient. The total cost is therefore £6,028,500/1000 patients or £6126 per life saved.

Table A1
Cost of surveillance programme at Charing Cross Hospital — cost of 10 year follow-up per patient

	Seminoma	NSGCT
38 clinic visits (£71/visit)	£2698	£2698
CXR (£15 each)	£510 (34 CXRs)	£540 (36 CXRs)
CT scan (£159 each)	£636 (4CTs)	£318 (2CTs)
Markers (£22 each pair)	£1056 (48 markers)	£1056 (48 markers)
Total	£4900	£4612

NSGCT, non-seminomatous germ cell tumours; CXR, chest X-ray; CT, computed tomography.

Table A2
Cost of salvage treatment with POMB/ACE chemotherapy

Chemotherapy	
POMB	£541.95
ACE	£207.24
Hospital costs	
Overnight stays (£300/night)	£2700
Day treatments (£100/day)	£600
Other costs (antiemetics, GCSF, antibiotics etc)	£500
Total	£4549.19

GCSF, granulocyte colony-stimulating factor.
POMB, ACE, see text (p. 1927) for definition.

Table A3
Cost comparison of surveillance, nerve sparing RPLND, adjuvant chemotherapy and radiotherapy over 10 years

	Treatment costs (per 1000 patients)			
	Surveillance	Nerve sparing RPLND	Adjuvant ChemoRx	Adjuvant RadioRx
Initial therapy	£4 756 000	£3 600 000	£1 925 000	£800 000
Follow-up		£3 145 000	£3 145 000	£3 296 000
Salvage chemotherapy (£4550/patient)	£1 137 500	£773 500	£364 000	£227 500
Salvage RPLND (£3600/patient)	£135 000		£288 000	
Total	£6 028 500	£7 518 500	£5 722 000	£4 323 500
Lives saved	984	980	978	985
Total per life saved	£6126/life saved	£7672/life saved	£5851/life saved	£4389/life saved

RPLND, retroperitoneal lymph node dissection; Adjuvant ChemoRx, adjuvant chemotherapy; Adjuvant RadioRx, adjuvant radiotherapy.

RPLND

For nerve sparing RPLND the cost of surgery is £3600. All patients will require surveillance following their RPLND. We have estimated that surveillance after RPLND would involve half as many clinic visits and CXR, but the same number of markers and CT scans as our routine surveillance programme and would cost £2993 for NSGT and £3296 for seminoma per patient. The average figure of £3145 has been used here. Combination chemotherapy would be required for the 17% who relapse. This totals £7 518 500/1000 patients i.e. £7672 per life saved.

Adjuvant chemotherapy

Adjuvant BEP chemotherapy (two cycles) costs £1925 per patient. In addition there is the cost of follow-up monitoring for relapse and for those who relapse (8%) the cost of salvage chemotherapy and RPLND. In total this is £5 722 000/1000 patients or £5851/life saved.

Adjuvant radiotherapy

Radiotherapy for stage I seminoma costs £800 per course (£800 000/1000 patients). Follow-up monitoring is required for relapse and the 5% who relapse will require salvage chemotherapy. This would total £4 323 500/1000 patients or £4389/life saved. These figures are summarised in Table A3.

The cost of various treatment options is under increasing scrutiny in medicine. The cost:benefit analysis performed in this paper aims to provide an approximation of the costs for the various treatment modalities, based on treatment at Charing Cross Hospital. These costs will vary between centres. We have halved the frequency of clinic visits and CXRs after RPLND, adjuvant chemotherapy and adjuvant radiotherapy compared with primary surveillance because it is advocated that these treatments have the advantage of requiring less frequent follow-up of patients after treatment. The cost analysis shows that a surveillance policy is certainly not more expensive than the other treatment modalities and, may in fact, be more cost-effective.

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