12 Year Review of Testicular Tumour Treatment by the Army Medical Services

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SUMMARY: Between 1977 and 1988 144 patients with tumours of testicular origin were referred to the Queen Elizabeth Military Hospital at Woolwich. 140 of these were malignant and all but two were treated and followed. Three of the malignant lesions appeared to be extragonadal. During the 12 year period staging has become increasingly accurate and treatment protocols have improved. These changes are reflected in this series. Ten deaths from tumour occurred (6.9%) but only one of these in the last three years of the study period despite an increasing case load at the time. The clinical presentation, treatment, and results of treatment are presented and the advances of treatment and improvement of prognosis discussed.

Introduction

Testicular cancer is uncommon, accounting for less than 1% of all cancers in the general population (1). Predominantly a disease of young males it is the commonest malignancy encountered in the Armed Forces after lymphoma. Testicular tumours are classified into two main groups namely seminoma and teratoma or non-seminomatous germ cell tumour (NSGCT).

Between 1977-1988 144 men with tumours of testicular origin were referred to the Queen Elizabeth Military Hospital (QEMH) for staging and further management. 140 were malignant and of these 138 were treated at QEMH in collaboration with the Oncology Department of Westminster Hospital, London.

Patients and Methods

The notes of 144 patients treated at the QEMH between 1977 and 1988 were traced from hospital records and the Army Histopathological Register (AHR) currently kept at the Royal Army Medical College, Millbank, London.

There were four patients with benign Leydig tumours which are excluded from further discussion, leaving a total of 140 malignant cases.

Orchidectomy was performed via the inguinal approach with division of the spermatic cord at the deep inguinal ring. Blood for the tumour markers alpha fetoprotein (AFP) and beta-human chorionic gonadotrophin (BHCG) was taken prior to operation.

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Fig 1. QEMH Testicular Tumours 1977-88.

Histological diagnosis was made at the hospital of presentation and the patients referred to the QEMH for staging and further management.

Fig 1 shows the number of cases referred to the QEMH by year. The number has increased in the last four years of the period studied; a total of 78 cases pre-

sented between 1985-88 inclusive compared with 66 in the previous eight years.

Patients presented with a variety of symptoms and signs. Pain was the presenting feature in 48% but swelling was the commonest symptom being noted in nearly 90% of cases. A history of trauma to the testis was obtained in 26 cases and of previous maldescent and/or orchidopexy in 20. Thirteen men had gynaecomastia and a further 9 (6%) had previously undergone vasectomy.

Patients with seminoma were older than those with teratoma. The average age of men with both seminomatous and teratomatous elements in their primary tumours was intermediate between the other two groups. The mean age of men with mixed primary tumours was 29.5 years compared to 26.2 ($p < 0.05$) and 33.3 ($p < 0.05$) for pure teratoma and seminoma respectively. No distinction is made between mixed tumours and pure teratomas in consideration of treatment and are therefore dealt with collectively in further discussion.

Classification was according to the British Testicular Tumour Panel (2). Tumours were staged according to the Royal Marsden Hospital staging classification (3).

Pre- and post-orchidectomy levels of AFP and β HCG, full blood count, erythrocyte sedimentation rate, urea, electrolytes and liver function tests were routinely estimated in all patients with histologically proven tumours of the testis at the time of this series. Chest X-ray, bipedal abdominal lymphangiography, abdominal ultrasound and radioisotope liver scanning also formed part of an extensive staging protocol but with the evolution and increasing accuracy of computerised scanning of the abdomen and thorax, arguments in favour of omitting lymphangiography (4), have led to abandonment of this investigation and radioisotope scanning of the liver.

In 26 cases pre-orchidectomy levels of AFP and β HCG were not measured. Of the remaining 114, 21 had raised preoperative AFP with normal β HCG levels; all teratomas (Table 1). One case, where the histology of the primary lesion, despite the elevated AFP, suggested pure seminoma and he was therefore treated as such. Twelve cases had raised β HCG with normal AFP levels; 6 seminomas, 6 teratomas. There were 34 patients with tumours producing elevated preoperative levels of both markers; 32 teratomas and 2 seminomas. Thus 67/114 patients (59%) had raised pre-operative tumour markers.

Table 1
Number of Testicular Tumour Patients with Raised Tumour Markers
(Queen Elizabeth Military Hospital 1977-88)

	AFP	β HCG	AFP + β HCG	Total (%)
Teratoma	20	6	32	58 (77)
Seminoma	1	6	2	9 (26)
TOTAL	21	12	34	67 (58)

Table 2
Staging of Types of Testicular Tumours
(Queen Elizabeth Military Hospital 1977-88)

Tumour	I	II	III	IV
Seminoma	31	8	3	2
Teratoma	37	28	7	24
TOTAL	68	36	10	26

Table 2 shows the number of cases in each histological subgroup and stage.

Treatment

One hundred and thirty eight malignant lesions of testicular origin were treated at QEMH:

Stage I

Twenty three of the 31 stage I seminomas were IA. One single patient whose AFP level began to rise following orchidectomy was staged IM. A raised AFP is generally regarded as consistent with a teratoma but rare instances have been reported when no teratomatous elements are present despite careful histological scrutiny as in this case (5). This man was treated with four courses of chemotherapy according to the method of Einhorn and Donohue (6) using cis-platin, vinblastine and bleomycin (PVB). The remaining seven patients were classified as stage IB. There were no deaths in this group of patients who remain disease free 22-164 months (median 74) following completion of all treatment.

Twenty-seven patients were originally staged as teratoma. Seventeen received radiotherapy to paraortic and ipsilateral iliac lymph nodes in doses of 3000-5000 cGy. One patient received PVB chemotherapy instead and the other 9 more recent cases were placed under close surveillance. One of these progressed with involvement of the abdominal lymph nodes and was restaged IIA. He responded completely to four courses of a combination of bleomycin, etoposide, cis-platin and vincristine (BEPV). This regime is briefly outlined in Table 3. There were four patients with stage IB tumours, one received radiotherapy to a dose of 3000 cGy, the others BEPV chemotherapy. Six patients with stage I teratomas were given the following treatment: Three were given 4 courses of BEPV, one was given PVB x 4 courses, one received two courses of BEPV and 4000 cGy radiotherapy and the last case had 4600 cGy plus a combination of vinblastine, bleomycin, cyclophosphamide and methotrexate (VBCM). All 37 stage I teratoma patients remaining, after the exclusion of the case that progressed whilst on surveillance, are alive and disease free 26-100 months (75) after treatment.

Stage II

There were 8 Stage II seminomas (five 2A, three 2B). Five received abdominal radiotherapy (3000 cGy). Two had BEPV chemotherapy followed by radiotherapy for residual lymph node masses, one of whom had excision

Table 3
BEPV Regime for Testicular Tumours
(Queen Elizabeth Military Hospital 1983-88)

DAY 1	Cis-platin Etoposide (VP 16) Vincristine	50 mg/m ² i.v. 120 mg/m ² i.v. 1.4 mg/m ² i.v.
DAY 2	Cis-platin Etoposide (VP 16) Bleomycin	50 mg/m ² i.v. 120 mg/m ² i.v. 15 mg/m ² i.v.
DAY 3	Etoposide (VP 16)	120 mg/m ² i.v.
DAY 9	Bleomycin	15 mg/m ² i.v.
DAY 16	Bleomycin	15 mg/m ² i.v.
21 day cycle. Day 22 = Day 1 of next course.		

of residual lymph node tissue which contained benign fibrosis histologically. The remaining patient had BEPV chemotherapy alone. (Follow up 75 months; range 51-120.)

All 27 patients with Stage II teratomas received chemotherapy. The 14/16 stage IIA patients received 4 courses of BEPV, the other two received PVB x 4 courses and 5000 cGy to the paraortic nodes plus VBCM x 3 courses respectively. 4/7 patients with stage IIB disease received 4 courses of BEPV, two had radiotherapy and PVB and one radiotherapy plus VBCM. There were four patients with large volume IIC tumours, three of whom responded to six courses of BEPV. The exception was rendered disease free by four courses of PVB. All patients in this group remain well 21-140 months following cessation of treatment (mean 61 months).

Stage III

The two patients with stage III seminomas, both of whom had large volume disease (IIIC), one presented with extragonadal primary disease and obtained complete response of his tumour to radiotherapy. The other man responded completely following 6 courses of PVB. Both remain free of disease 35 and 96 months after completion of treatment respectively.

There were seven patients with stage III teratomas. Two were classified IIIA and both responded completely to 4 courses of BEPV. The remaining 5 were staged IIIC. Three received PVB and radiotherapy one of whom died as the result of massive mediastinal disease. The remaining two patients were treated with PVB and BEPV respectively and both obtained a complete response. The six survivors remain well at 80 months (range 45-108).

Stage IV

There were two patients with stage IV seminoma one of whom died from widespread metastatic disease including the cerebellum and bone marrow. He failed to respond despite PVB chemotherapy x 3 courses plus ra-

diotherapy to the brain. The other patient received 4000 cGy radiotherapy to a large paraortic mass followed by 2000 cGy to the left lung when two secondary deposits appeared plus a further 4000 cGy to a supraclavicular mass. Further treatment in the form of three courses of vincristine, actinomycin D and cyclophosphamide (VAC) was required to treat an almost immediate recurrence of further lung metastases. A year later bleomycin was instilled into both pleural spaces when he developed bilateral effusions. This patient remains alive and well 89 months after completion of all treatment and is assumed to be disease free despite the presence of lung opacities believed to be 'sterile' on CXR. The patient has marked pulmonary fibrosis clinically and radiologically.

24 patients were found to have stage IV teratoma on investigation and 8 deaths occurred in this group. One died on the day of admission of advanced MTI from haemorrhage into a cerebral metastasis before he could receive any treatment. Twelve patients received 4-6 courses of BEPV alone, three of whom died despite second line chemotherapy. A further patient received BEPV but required the addition of 5500 cGy irradiation for a cerebral metastasis following urgent decompression and debulking for haemorrhage into a parietal lobe deposit. He is our only survivor with cerebral secondaries which in our experience carries a particularly poor prognosis. Three patients received 4 courses of PVB alone; all are well. Three were treated with PVB with the addition of local radiotherapy for abdominal and/or chest masses. All three of these patients died of overwhelming metastatic disease. A further patient received methotrexate and chlorambucil in addition to PVB and remains well. Another patient died of massive lung, abdominal and hepatic metastases despite PVB with second line chemotherapy in the form of etoposide, adriamycin and DTIC. The three remaining patients in this group received odd combinations of chemotherapeutic agents; one VBCM plus radiotherapy who survives 134 months following the completion of treatment, one patient in the early part of our series received three courses of vinblastine and bleomycin followed by three courses of etoposide in addition to 1600 cGy to the lungs for pulmonary secondaries. This treatment was in turn followed by six courses of a combination of cyclophosphamide and actinomycin with finally 12 courses of chlorambucil and methotrexate. He remains well 129 months post treatment. The average length of follow up in the 16 survivors in this group is 74 months with a range of 30-134. These data are summarised Tables 4 and 5.

Discussion

Early diagnosis of a testicular swelling is essential to confirm or refute the presence of tumour. However, 16% of our cases had primary treatment delayed by over a month because of slow referral. A further 44% were responsible for a similar length of delay due to failure to

Table 4
Treatment of Patients with Testicular Teratoma
(Queen Elizabeth Military Hospital 1977-88)

	I	II	III	IV
Surveillance	8	(1)		
Radiotherapy	19			
Chemotherapy	8	23	4	17
Chemotherapy +	2	4	3	3
Radiotherapy				
Chemotherapy +				3
Radiotherapy +				
Surgery				
No treatment*		1		1
Total	37	28	7	24

*one patient died without treatment the other was treated elsewhere.

The patient in parenthesis disease progressed to stage IIA whilst on surveillance and received chemotherapy.

Table 5
Treatment of Patients with Testicular Seminoma
(Queen Elizabeth Military Hospital 1977-88)

	I	II	III	IV
Radiotherapy	30	5	1	
Chemotherapy	1	1	1	
Chemotherapy +		1		2
Radiotherapy				
Chemotherapy +		1		
Radiotherapy +				
Surgery				
Total	31	8	2	2

report symptoms. We were unable to correlate delay of diagnosis with outcome although concern about delays has been highlighted elsewhere (7). It has been suggested that public awareness, education in self-examination and immediate reporting of testicular swellings might make an impact on survival (8).

Testicular neoplasms can present with visceral metastases with a small and even clinically undetectable, primary. In our series 21 primary tumours were reported as 20 mm diameter or less; ten of which were stage III or IV. The size of the primary, however, bears no relation to stage of disease. Earlier diagnosis should be possible with the increasing use of ultrasound scanning of the testicle which in our experience has shown a very high degree of accuracy in distinguishing between benign disease and tumour. However, if any doubt still remains as to the nature of a testicular swelling exploration is mandatory.

The staging of testicular tumours has become increasingly accurate over the period of this study with increasingly sophisticated investigation techniques. CAT Scanning (CT) of the thorax and abdomen has been added to our staging protocol that has evolved with each

new development. We are thus able to compare CT scanning with lymphangiography, ultrasonography and radioisotope scanning. Each has its value but it is questionable whether all these investigations are now necessary (4).

Advances in treatment of testicular tumour have improved prognosis over the last 15 years to the degree that a zero mortality rate is a reasonable objective. In a series of 275 patients reported from the Royal Marsden Hospital (9) between 1962-75, 48% remained alive in 1977. Fifty six per cent had disease confined to the testicle and this group comprised most of the survivors. Fifteen per cent of patients with stage III or IV disease were alive and disease free highlighting the poor outlook during this period for patients with metastatic disease.

Early results with single agent chemotherapy were not encouraging; A review of the literature to 1972 (10) found only 31 cases of metastatic testicular tumour in complete remission, 17 of which were treated with mithramycin. Samuels et al (11-13), produced encouraging results using two different vinblastine bleomycin (VB) combination regimes in MTU and combination of bleomycin, cyclophosphamide, vincristine, methotrexate and 5-fluouracil (bleoCOMF) in addition to VB in MTI. The best of the VB regimes produced complete response rates of 58% of 36 patients with MTU. 10/24 (42%) patients with MTI treated with VB/bleoCOMF responded completely and only one relapsed. VB failed to produce complete remission in 10 patients with MTT. Further progress occurred with the addition of cis-platin to vinblastine and bleomycin by Einhorn & Donohue (6).

The advances in treatment are reflected in this series and treatment schedules underwent change over the 12 year period. Prior to 1986 all patients with Stage IA and IB malignant neoplasms were given prophylactic radiotherapy to the ipsilateral iliac and the entire paraortic chain of lymph nodes. Since 1986 stage IA teratomata have been placed under close surveillance and have only been treated if they have shown signs of progression. Stage IB or IM cases have received chemotherapy. Patients with seminoma have continued to receive prophylactic nodal radiotherapy to a dose of 3000 cGy.

In the years preceding the platinum containing regimes a variety of chemotherapeutic agents was employed, in combination, usually containing some of the following: cyclophosphamide, vinblastine, bleomycin, methotrexate, chlorambucil and/or adriamycin. There were four cases who fell into this category, all of whom survive.

From 1980-83 PVB chemotherapy was used routinely for metastatic tumour and in 22 cases so treated there were 6 deaths from tumour all presenting with advanced disease representing a 72.7% complete remission rate. This compares favourably with the Einhorn and Donohue's series where in 47 cases there was 74%

complete response rate. Their patients were divided into five groups, A-E, A, C and E denoted minimal pulmonary disease, minimal pulmonary and abdominal disease and elevated β HCG respectively. Groups B and D referred to advanced pulmonary and abdominal tumour. Using these criteria for comparison only 4/22 of our patients had minimal disease all of whom achieved complete remission compared to 22/47 of whom 20 survived. There were 6 deaths out of our remaining 18 patients (33%) with advanced disease in contrast to 9/25 (36%) in the original series.

Since 1983 we have used BEPV as first line treatment in metastatic disease. Presently 44/47 cases (96%) are alive and disease free 12-75 months following completion of treatment (14). In an earlier series from the Royal Marsden (15) using a similar combination without vincristine (BEP) 93% were reported alive and well with 86% disease free 8-38 months from commencement of treatment. We reserve radiotherapy for residual disease following chemotherapy as the Royal Marsden group have demonstrated a markedly increased morbidity when radiation is given first. It remains to be seen whether BEPV represents a significant improvement over BEP and study of larger numbers is required.

In conclusion the prognosis for advanced metastatic testicular tumour has been transformed over the past 15 years. The aim for the future must be to achieve as near to zero mortality as possible, whilst at the same time reducing treatment toxicity by the adoption of a surveillance policy in selected patients and improvements in systemic therapy for those who need it.

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