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ORIGINAL ARTICLE **CME**

Retrospective Clinico-pathological Study of Germ Cell Tumours Managed in a Single Institution

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ABSTRACT

Objective: *To study the clinico-pathological characteristics and outcome of germ cell tumours treated in the Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong.*

Methods: *This was a single-institution retrospective review of patients with extrancranial, non-ovarian germ cell tumours treated in the department from 1995 to 2004. Clinico-pathological characteristics and outcome were analysed. Overall, cause-specific, and event-free survivals were evaluated by the Kaplan-Meier method and compared using the log rank test.*

Results: *In all, 110 male patients were followed up for a median of 8 years. Their median age was 33 (range, 17-79) years. Ninety-eight (89%) of the patients had a testicular primary, and 12 (11%) had mediastinal primaries. Seventy-two (65%) were seminomas, and 38 (35%) were non-seminomas. The mean 5-year overall survivals for patients with stage I, II, and III testicular tumour were 100%, 92%, and 81%, respectively. The mean 5-year overall survival for patients with mediastinal primaries was 75%. For stage I seminoma, 29 (62%) of the patients were managed by chemotherapy, 11 (23%) by radiotherapy, 2 (4%) by sequential chemotherapy and radiotherapy, and 5 (11%) by surveillance; all of whom survived 5 years. For advanced germ cell tumours, the respective mean 5-year overall survivals were 90%, 100%, and 36% for patients classified as having a good, intermediate, and poor prognosis (according to the International Germ Cell Cancer Collaborative Group prognostic grouping).*

Conclusion: *Patients having early-stage germ cell tumours have an excellent prognosis with a high cure rate. The outcome of patients having an International Germ Cell Cancer Collaborative Group classified as poor, remains unfavourable. Overall, the treatment outcome in our cohort was comparable to the global experience.*

Key Words: *Bleomycin; Cisplatin; Etoposide; Neoplasms, germ cell and embryonal; Prognosis*

中文摘要

單一機構治療生殖細胞腫瘤的臨牀病理回顧分析

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目的：研究香港伊利沙伯醫院臨床腫瘤科診治的生殖細胞腫瘤的臨牀病理特徵及預後。

方法：是項單一機構回顧性分析的研究對象為1995年至2004年間，於上述部門接受治療的顱外非卵巢生殖細胞腫瘤患者。對臨床病理特徵和治療效果進行分析，以Kaplan-Meier方法評估整體存活率、特定病因存活率和無併發症存活率，用log rank test比較上述三種存活率。

結果：研究共110名男性患者，隨訪中位數為8年；病人年齡中位數為33歲（介乎17-79歲）。98名（89%）患者為原發睾丸癌，12名（11%）為原發縱隔腫瘤。72名（65%）患有精原細胞瘤，其餘38名（35%）則患有非精原細胞瘤。第一、二、三期睾丸癌的平均5年整體存活率分別為100%、92%和81%；原發縱隔腫瘤患者則為75%。在第一期精原細胞瘤患者中，29名（62%）進行化療、11名

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（23%）採用放射治療、2名（4%）則使用連續化療和放射治療，而其餘5名（11%）只進行觀察；全部均可存活5年。根據國際生殖細胞腫瘤合作小組的分類標準，在末期生殖細胞腫瘤患者中，被界定為「預後良好」、「預後中等」和「預後惡劣」的，其平均5年整體存活率分別為90%、100%和36%。

結論：早期生殖細胞腫瘤患者有良好預後，治癒率也較高；但根據上述疾病分類標準屬「預後惡劣」的患者，其治療效果仍不甚理想。總括而言，這項研究的治療結果與全球治療經驗相若。

INTRODUCTION

Germ cell tumours arise mostly in men. They are thought to be derived from primitive germ cells with arrested maturation, most commonly in the testis which could be intrascrotal or maldescended at any site. Alternatively, they may be in the retroperitoneum, mediastinum, suprasellar or pineal regions. Germ cell tumours are classified into seminomatous and non-seminomatous types, and are characterised by a chromosomal marker i(12p), which is found in a high proportion of cases irrespective of the primary site or the pathological type.

Testicular germ cell tumours are quite common and account for about 1% of all malignancies in males. Data from the Hong Kong Cancer Registry in 2006 showed that the incidence was 1.6 per 100,000 male inhabitants per year, which translates into about 56 new cases annually.[1]

Testicular germ cell tumours are important cancers despite their rarity. They mostly affect men aged 20 to 39 years, and constitute the most common cancer afflicting young adult men. With the advent of cisplatin-based chemotherapy that improves the chance of cure even in advanced disease since the 1970s, the overall long-term cure rate has increased to over 80%.[2-4] The management of germ cell tumours is highly specialised, and requires expertise in radiology, surgery, and oncology to form a multidisciplinary team approach. Treatment in specialist centres is associated with better outcomes.[5-7]

This study aimed to evaluate the clinico-pathological characteristics and outcomes of testicular and mediastinal germ cell tumours treated in a local Chinese male population in comparison to global experience. Central nervous system and ovarian germ cell tumours are outside the scope of this study, as the management strategy for these tumours is quite different.

METHODS

This was a single-institution retrospective review of patients referred to the Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong for treatment from January 1995 to December 2004. In all, 110 patients with testicular or mediastinal germ cell tumours were identified. No patient was diagnosed to have a retroperitoneal primary germ cell tumour. The medical records of these patients were reviewed and data extracted for analysis.

After referral to our department, the patients had undergone investigations for staging and assessment of fitness for treatment. These included: blood tests for complete blood count, liver and renal function, tumour markers of alpha-fetoprotein, beta-human chorionic gonadotropin and lactate dehydrogenase, and hepatitis B status. Imaging studies included ultrasound of the scrotum and computed tomography (CT) of the thorax, abdomen, and pelvis. Lung function test and semen analysis were also performed. The option of sperm banking was discussed with patients as indicated. Treatment was planned based on each patient's fitness, preference, and disease status.

In our department, patients with stage I testicular seminoma were offered adjuvant chemotherapy with 2 cycles of carboplatin (area under curve [AUC] = 6) or adjuvant para-aortic radiotherapy (RT). For those with stage I non-seminoma, 2 cycles of adjuvant BEP360 (bleomycin 30 mg on days 1, 8 and 15; etoposide 120 mg/m^2 on days 1-3; cisplatin 20 mg/m^2 on days 1-5) were given. Patients who were reluctant to have adjuvant treatment were kept under surveillance.

Patients with stage IIA testicular seminoma were treated with RT or 3 cycles of BEP chemotherapy. For those with more advanced disease or a mediastinal primary, treatment was based on the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic group recommendations. We offered BEP500 (bleomycin 30 mg on days 1, 8 and 15; etoposide 100 mg/m^2 on days 1-5; cisplatin 20 mg/m^2 on days 1-5) for 3 cycles to those with a good prognosis, and 4 cycles to those with an intermediate or poor prognosis. There might have been variation from this general treatment policy for

individual patients, depending on clinical circumstances and the judgement of the physician in-charge.

The data were analysed using the Statistical Package for the Social Sciences (Windows version 15). Categorical data were compared using the chi-square test, and continuous data by the *T*-test. The Kaplan-Meier method was employed for survival analyses. The log-rank test was used for univariate analyses. Overall survival (OS), cause-specific survival (CSS), and event-free survival (EFS) were evaluated. EFS was defined by the time interval between the diagnosis and the occurrence of any event (relapse, failure to achieve complete remission after treatment, or disease progression).

RESULTS

Baseline Characteristics

There were 110 patients, all of them were male; 98 (89%) of them had testicular germ cell tumour and 12 (11%) had mediastinal germ cell tumours. The mean age at diagnosis was 35 and 26 years, respectively ($p = 0.004$). For the whole group of patients, the median age at diagnosis was 33 years and the median follow-up period was 8 years.

Risk factors for germ cell tumour development among those with testicular primaries were explored. Twenty-five (26%) of the patients had a history of undescended testis; 27 (28%) were found to have testicular intraepithelial neoplasia in their pathology specimen. Among those who had semen analysis performed, 29 (88%) had oliogospermia or azospermia. Only 1 (1%) out of 98 patients had a family history of testicular neoplasm.

With regard to pathology, 72 (65%) of the patients had seminomas and 38 (35%) had non-seminomas. There was no significant difference in the seminoma/non-seminoma proportion in the testicular and mediastinal tumours ($p = 0.58$). Among the 36 patients with non-seminomas with known histology, 11 (31%) had a pure histology, and 25 (69%) had mixed histological subtypes. Embryonal carcinoma was the most common histological subtype among patients with non-seminoma, followed by teratoma seminoma, yolk sac histology, and choriocarcinoma.

Clinico-pathological Features

Testicular Germ Cell Tumour

There were 47 patients with tumour in the left testis, 49 with tumour in the right testis, and 2 with bilateral testicular involvement. Of these patients, 79 (81%) presented with a painless testicular mass; 12 (12%) presented with a painless abdominal or groin mass; 5 (5%) presented with pain in the abdomen, back or groin area; and the remaining 2 (2%) were asymptomatic.

Sixty-six (67%) of the patients had UICC (International Union against Cancer) stage I disease, 12 (12%) had stage II, 18 (18%) had stage III, and 2 (2%) could not be classified. More patients with non-seminomas presented with metastatic disease and abnormal tumour marker levels (28% and 81%, respectively) compared to seminomas (2% and 45%, respectively) [$p < 0.001$]. Ten patients had distant metastases. Only one of them was a seminoma, having a lung metastasis only. Among the 7 non-seminomas with M1a disease, 3 had lung and distant lymph node metastases, 1 only had a single distant lymph node metastasis, and 3 had lung metastases alone. For the 2 non-seminoma patients who had M1b disease, 1 had lung, liver and distant lymph node metastases, and the other had liver and brain metastases.

In all, 97 patients had orchidectomies and 1 only had a biopsy as initial management before being referred to our department. The latter patient underwent chemotherapy and RT followed by an inguinal orchidectomy.

Table 1. Pathological characteristics of testicular germ cell tumour.

Characteristic	Seminoma	Non-seminoma	p Value
Tumour size			
Mean (cm)	7	5	
Range (cm)			
>4	49 (79%)	17 (53%)	0.0093
≤4	13 (21%)	15 (47%)	
Unknown	3	1	
Vascular invasion			0.21
Yes	14 (22%)	11 (33%)	
No	51 (78%)	22 (67%)	
Rete testis involvement			0.99
Yes	2 (3%)	1 (3%)	
No	63 (97%)	32 (97%)	

Table 2. IGCCCG prognostic groups for stage II/III testicular and mediastinal germ cell tumour.

Group	Prognostic groups			
	Good	Intermediate	Poor	Unknown
Seminoma				
Total	24 (100%)	0	-	0
Testis	17	0	-	0
Mediastinal	7	0	-	0
Non-seminoma				
Total	6 (33%)	4 (22%)	7 (39%)	1 (6%)
Testis	6	4	2	1
Mediastinal	-	-	5	0

Abbreviation: IGCCCG = International Germ Cell Cancer Collaborative Group.

Table 3. Treatment for stage I testicular germ cell tumours.

Treatment	Seminoma	Non-seminoma
Treatment modality		
Surveillance	5 (11%)	1 (5%)
Chemotherapy	29 (62%)	18 (95%)
Radiotherapy	11 (23%)	-
Both	2 (4%)	-
Chemotherapy scheme		
Carboplatin	29 (94%)	-
BEP	2 (6%)	18 (100%)
Radiotherapy site		
Dogleg	11 (84%)	-
Dogleg and scrotal	1 (8%)	-
Others	1 (8%)	-

Abbreviation: BEP = bleomycin, etoposide, cisplatin.

Six (6%) of the 97 patients had scrotal violation. Clear resection margins were achieved in 92 (94%) of the patients. The mean tumour size was 7 cm for seminomas and 5 cm for non-seminomas. Pathological characteristics, including vascular invasion and rete testis involvement, are shown in Table 1.

Among those with stage I seminomas, 33 (75%) of the patients had tumour sizes greater than 4 cm, 1 (2%) had rete testis invasion, 10 (23%) did not have any of these risk factors, and none had both risk factors simultaneously. Among patients with stage I non-seminoma, 3 (16%) revealed vascular invasion.

Mediastinal Germ Cell Tumour

There were 12 patients with mediastinal germ cell tumours, all presenting with superior vena cava obstruction or shortness of breath. Three patients had metastatic disease, all of which were non-seminomas. Two of them had lung metastasis only, and 1 had lung and spleen metastases.

International Germ Cell Cancer Collaborative Group Classification

Forty-two patients with mediastinal germ cell or testicular germ cell tumours with nodal or distant metastases were classified according to the IGCCCG consensus classification criteria into good, intermediate, or poor prognostic groups.[8] All seminoma patients in our study belonged to the good prognostic group. Details are shown in Table 2.

Treatment

Table 3 shows treatments given to patients with stage I testicular germ cell tumours. Among the 29 patients with stage I seminoma who were given chemotherapy alone, 28 received carboplatin. The remaining patient, with bilateral tumours of both undescended testes with extension to pelvic sidewall and retroperitoneum compressing on the bladder, was given BEP (bleomycin, etoposide, cisplatin). Eleven patients received RT alone, 30 Gy in 15 fractions of which 10 were treated with the dogleg field and 1 with dogleg plus scrotal RT. Among the two who received both chemotherapy and RT, one patient had cytoreductive pelvic RT (12 Gy in 6 fractions) then BEP for 4 cycles, followed by definitive orchidectomy (showing necrosis). The other patient refused further RT after 22 Gy/11 Fr, and was given 1 cycle of carboplatin (AUC 6). Five patients did not receive any postoperative treatment and were put under surveillance. For stage I non-seminoma patients, 18 received chemotherapy with BEP, and one was put on surveillance.

Among the 42 patients with nodal or distant metastatic testicular or mediastinal germ cell tumours, 40 received chemotherapy. Of the latter, 35 patients received BEP, and 4 received POMB/ACE (cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide), and 1 received EP/OMB (etoposide, cisplatin, vincristine, methotrexate, bleomycin). Of the 2 patients who were not given chemotherapy, 1 had a stage IIA (T3N1M0S1) seminoma and was treated by RT to 40 Gy in 20 fractions with an inverted-

Y field. The other patient with a stage IIIB (T2N0M1aS2) seminoma refused any treatment and died 1 year later.

Nine patients (5 testicular seminomas, 2 testicular non-seminomas, and 2 mediastinal non-seminomas) failed to achieve complete remission after first-line chemotherapy, with 2 of them having static disease and 7 had a partial response. All of them had normalised or plateau tumour markers after treatment, and underwent resection of residual masses. The pathology showed necrosis in 7 patients and viable tumour cells in 2. The resection margin was clear in 8 patients. The residual mass was incompletely removed in the remaining patient whose pathology showed necrosis. Among the patients with viable tumour cells, 1 was given further 2 cycles of consolidation VIP chemotherapy (etoposide, ifosfamide, cisplatin).

Of the 89 patients who received chemotherapy, neutropenic fever occurred in 6 (7%). Eighteen patients (15 with BEP and 3 with POMB/ACE) were given granulocyte-colony stimulating factor as primary or secondary prophylaxis. Eight patients (6 BEP, 1 carboplatin, 1 POMB/ACE) had dose reductions prompted by marrow toxicity. Of the 85 who had hepatitis status checked, 11 (13%) were hepatitis B carriers. Ten hepatitis B carriers received chemotherapy without lamivudine prophylaxis, 5 (50%) of whom were complicated by a hepatitis B flare-up that resolved with lamivudine treatment.

Regarding long-term treatment toxicity, no secondary malignancy was encountered. One patient died of congestive heart failure, but he had known dilated cardiomyopathy. No other significant cardiac event was identified in the cohort. Of the 101 patients who received treatment with chemotherapy or RT, 7 reported having children thereafter.

Outcome

Twelve events were recorded, all of which occurred within 2 years from the diagnosis. Four patients with testicular seminomas relapsed, as did 1 with mediastinal

Table 4. Summary of the clinical characteristics and outcomes of patients with events.

Patient No.	Primary site	Histology	Stage	Site of metastasis	Stage grouping	IGCCCG group	Initial treatment
1	Testis	Seminoma	T3N0M0Sx		I		Surveillance
2	Testis	Seminoma	T1N0M0S1		I		Surveillance
4	Testis	Seminoma	T1N0M0S1		I		Carboplatin (AUC 6) x 2
9	Testis	Seminoma	T1N3M0S2		III	Good	BEP x 3
3	Testis	NSGCT	T2N1M1aS1	Lung	III	Good	POMB/ACE x 3
5	Testis	NSGCT	T1N3M1bS3	Liver and	distant LN	III	Poor
6	Testis	NSGCT	T2N1M1aSx	Lung	III	Not classified	BEP x 4
8	Testis	NSGCT	T1N0M1bS3	Liver, lung, brain	III	Poor	EP/OMB x 6
7	Mediastinum	NSGCT	M1aS3	Lung		Poor	POMB/ACE x 4
10	Mediastinum	NSGCT	M1bS3	Spleen		Poor	BEP/POMB/ACE/EP x 6
11	Mediastinum	NSGCT	S2			Poor	BEP x 4 then resection of residual mass (viable) then consolidation VIP
12	Mediastinum	NSGCT	M1aS3	Lung		Poor	VIP

Abbreviations: ABMT = autologous bone marrow transplant; AUC = area under the curve; BEP = bleomycin, etoposide, cisplatin; CR = complete remission; EP/OMB = etoposide, cisplatin, vincristine, methotrexate, bleomycin; GJ = gemcitabine, carboplatin; HDCT = high-dose chemotherapy with autologous bone marrow/peripheral blood stem cell transplant; IGCCCG = International Germ Cell Cancer Collaborative Group; IT MTX = intrathecal methotrexate; LN = lymph node; NSGCT = non-seminomatous germ cell tumour; PA LN = para-aortic lymph node; POMB/ACE = cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide; PR = partial remission; RT = radiotherapy; SD = static disease; SVC = superior vena cava; TIP = taxol, ifosfamide, cisplatin; TJ = taxol, carboplatin; VeIP = vinblastine, ifosfamide, cisplatin; VIP = etoposide, ifosfamide, cisplatin.

non-seminoma. Seven patients with non-seminomas (4 testicular and 3 mediastinal) failed to achieve complete remission or had disease progression. No event was reported among those with mediastinal seminomas. Table 4 is a summary of the clinical characteristics and outcomes of patients who had events.

There were 11 deaths; 8 patients died of their disease, of which 7 had preceding events as shown in Table 4. The remaining patient with a testicular seminoma (T2N0M1aS2 disease) who refused treatment died at 1 year after the diagnosis. Three patients died of unrelated causes, 1 of concomitant chronic lymphocytic leukaemia 3 months post-diagnosis of germ cell tumour, 1 from necrotising fasciitis at 7 years after the diagnosis, and another (with a known dilated cardiomyopathy) died of congestive heart failure at 2 years post-diagnosis.

Survival analyses in terms of OS, CSS and EFS are shown in Table 5. The 5-year OS, CSS, and EFS for the whole patient cohort were 92%, 94%, and 88%, respectively. Univariate analysis was performed by the log-rank test, and yielded seminoma as faring significantly better than non-seminoma patients in terms of 5-year CSS (97% vs 89%; $p = 0.012$) and EFS (94% vs 78%; $p = 0.011$). Testicular primaries were associated with better outcomes than mediastinal primaries in terms of 5-year OS (95% vs 75%; $p = 0.004$), CSS (97% vs 75%; $p < 0.001$), and EFS (91% vs 67%; $p = 0.006$). The M-stage and S-stage were also significant factors predicting OS, CSS, and EFS.

For testicular primary tumours, the 5-year CSS were 100% for stages I and II, and 81% for stage III ($p < 0.001$), whereas the 5-year EFS values were 95%, 100%, and 71% for stages I, II and III, respectively ($p = 0.002$).

For stage I testicular seminoma parients, there was a significant difference in terms of EFS ($p = 0.001$) for different management options, with surveillance giv-

Event	Event detail	Time to event (years)	Salvage treatment	Time to last follow-up (years)	Status at last follow-up
Relapse	rN2	2.01	BEP	9.8	Alive without disease
Relapse	rN2	0.43	BEP	7	CR after salvage; died of necrotising fasciitis
Relapse	rN1	1.61	BEP (PR) → RT to abdomen/pelvis	3.13	Alive with liver and bone metastasis (defaulted follow-up)
Relapse	rN1	0.72	TJ, oral VP16, VIP (suboptimal dose intensity as patient refused treatment repeatedly)	2.08	Died of disease
Progression	Marker	0.22	VIP (CR) → HDCT	12	Alive without disease
BEP x 4	Failed CR	0.24	VIP → TIP → PA LN resection (incomplete resection) → TJ → GJ	0.84	Alive with disease (defaulted follow-up)
Failed CR		1.08	VeIP (PR) → lung resection (>95% resected)	5.08	Died of disease
Failed CR		0.33	VIP/IT MTX (marker CR) → resection of multiple lung nodules → HDCT → TJ	1.19	Died of disease
Progression		0.29	VIP (SD) → HDCT (SD) → mediastinal mass resection (SVC tumour thrombus unresected; pathology showed mature teratoma and chemo effect) → postop mediastinal RT 40 Gy/20 Fr	6.05	Died of disease (liver metastasis – transformation into poorly differentiated carcinoma) 5 years after HDCT
Progression		0.36	ABMT x 2 → VIP	1.25	Died of disease
Relapse	Local and lung	0.65	-	0.66	Died of disease
Progression		0.03	-	0.03	Died of disease after 1 day of chemotherapy

Table 5. Outcomes of patients with germ cell tumours.

Outcome	No.	Overall survival (%)		p Value	Cause-specific survival (%)		p Value	Event-free survival (%)		p Value
		5-year	10-year		5-year	10-year		5-year	10-year	
All patients	110	92	88		94	92		88	88	
Histology										
Seminoma	72	94	92	0.127	97	97	0.012	94	94	0.011
Non-seminoma	38	89	81		89	81		78	78	
Primary site										
Testis	98	95	92	0.004	97	95	<0.001	91	91	0.006
Mediastinum	12	75	64		75	64		67	67	
Site of metastasis (M-stage)										
Nil	94	97	95	<0.001	99	99	<0.001	95	95	<0.001
Lung only	10	79	56		79	56		56	56	
Extrapulmonary	3	50*	-		50*	-		-†	-	
Unknown	3	-	-		-	-		-	-	
Marker level (S-stage)										
S0	42	100	100	<0.001	100	100	<0.001	97	97	<0.001
S1	39	97	94		100	100		95	95	
S2	17	75	75		80	80		87	87	
S3	6	42‡	-		41.7‡	-		17‡	-	
Unknown	6	-	-		-	-		-	-	
Testicular primary										
Stage I	66	100	97	0.004	100	100	<0.001	95	95	0.002
Stage II	12	91	91		100	100		100	100	
Stage III	18	81	75		81	75		71	71	
Unknown	2	-	-		-	-		-	-	
IGCCCG prognostic groups										
Good	30	90	90	<0.001	93	93	<0.001	93	93	<0.001
Intermediate	4	100	100		100	100		100	100	
Poor	7	36	-		36	-		14§	-	
Unknown	1	-	-		-	-		-	-	

Abbreviation: IGCCCG = International Germ Cell Cancer Collaborative Group.
* Censored at 1.2 years.
† All had events by 0.36 years.
‡ All censored at 9.7 years.
§ 4-year figure listed as all patients censored at 4.4 years.

ing a worse 5-year EFS of 50% compared to the 97% achieved with adjuvant chemotherapy, and 100% with adjuvant RT or chemotherapy plus RT. The EFS curves are shown in Figure 1. Five-year CSS, however, was 100% for all management options, as those who failed with surveillance were successfully salvaged with chemotherapy. For patients with stage I testicular non-seminoma, no event or death was recorded.

For advanced germ cell tumours, the 5-year OS was 90%, 100% and 36% for good, intermediate, and poor IGCCCG prognostic groups, respectively (Figure 2).

DISCUSSION

The baseline clinico-pathological characteristics of our patient cohort were quite typical. The median age at diagnosis was 33 years, and most (89%) had testicular primaries. The proportion with mediastinal primaries (11%) was comparable to the 5 to 10% in the literature. Seminoma was the more common histology, accounting for 65%. This was the same as in a previous local series of 149 patients encountered in 1981 to 1992 reported by Chan et al,[9] and slightly higher than the 55% reported from the UK Royal Marsden Hospital in 649 patients seen between 1994 and 2003.[10] As in the Royal Marsden series, our series also showed that embryonal carcinoma was the most common non-seminomatous element, and non-seminoma was associated with a less favourable stage distribution compared to seminoma. The 5-year OS of our cohort of patient was 92%, which paralleled that of the global experience of a more-than-80% cure rate.[2-4]

This study covered patients treated between 1995 and 2004. Since then, new evidence has emerged, and there have been some changes to treatment policy in our department. In this study, those who received RT for stage I seminoma were all treated before 2001, and were

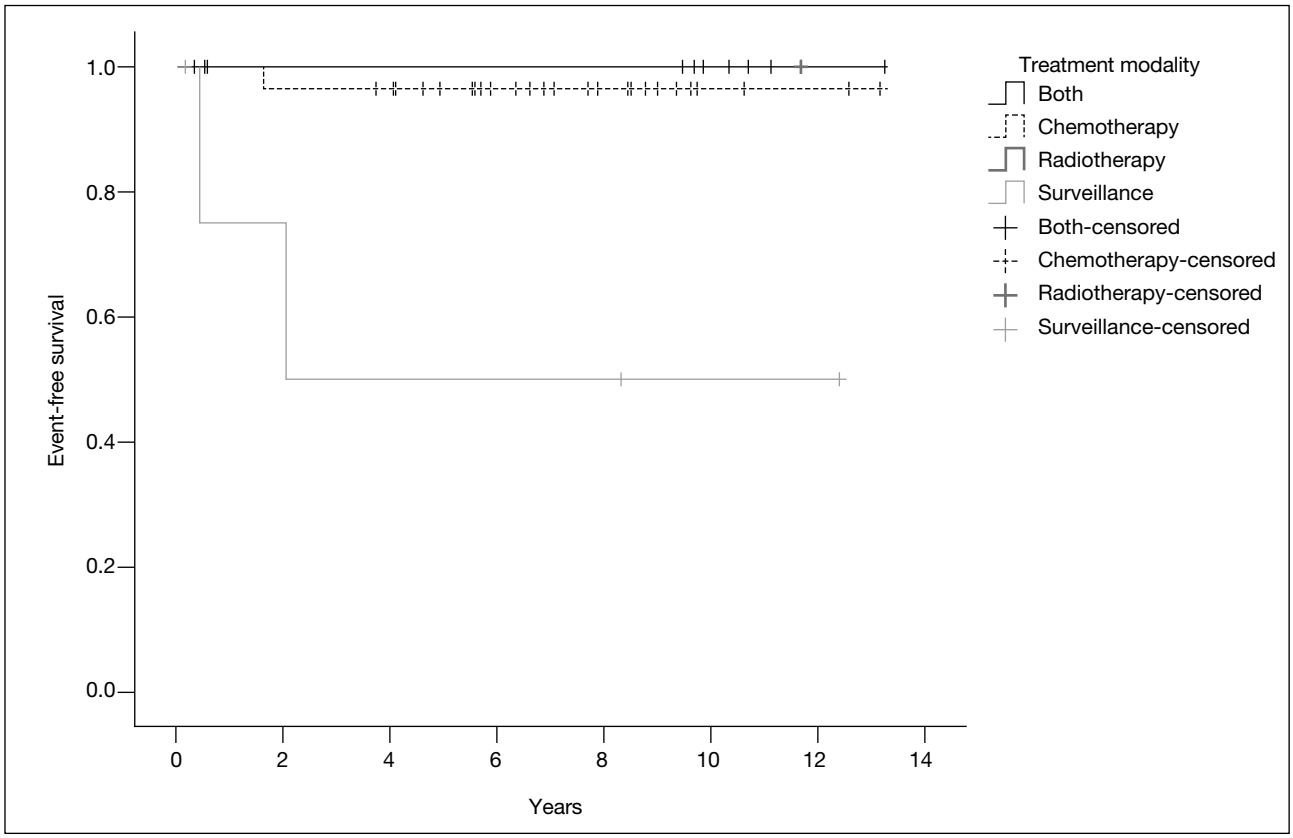

Figure 1. Event-free survival for stage I seminoma according to management strategy.

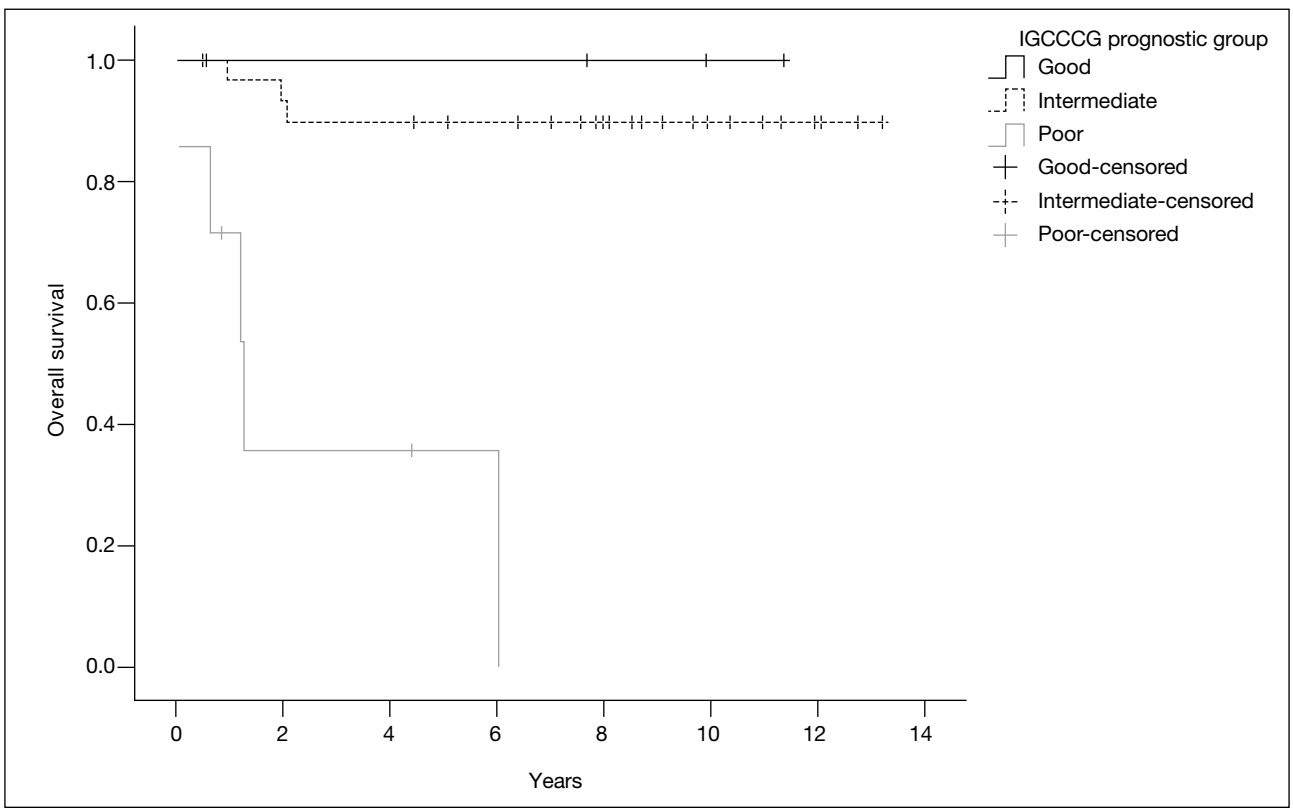

Figure 2. Overall survival for advanced germ cell tumour according to the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic groups.

treated with dogleg fields to a dose of 30 Gy. With the publication of 2 studies — the Medical Research Council TE 10 trial in 1999,[11] which showed that para-aortic field RT was not significantly different from dogleg RT in outcome but was associated with less side-effects; and the Medical Research Council TE 18 trial[12] which showed 20 Gy was as effective as 30 Gy but had less side-effects — the current accepted radiotherapy treatment would consist of para-aortic field RT to a dose of 20 Gy.

For advanced testicular or mediastinal germ cell tumour, BEP is the standard treatment. Before the era of cisplatin-based chemotherapy, combinations of vinblastin, dactinomycin and bleomycin resulted in OS rates of less than 10%.[13] With the use of BEP since the mid-1980s for advanced germ cell tumours, the OS rates have improved to 70 to 80%.[2-4] This is also reflected in our series with a 5-year OS of 81% for stage III disease. For advanced non-seminoma, 5 of our patients were given POMB/ACE (cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide) or EP/OMB (etoposide, cisplatin, vincristine, methotrexate, bleomycin) regimen, and the majority received BEP. There were phase II studies exploring the use of POMB/ACE in IGCCCG poor-prognosis patients in an attempt to improve outcome, and achieved a 3-year OS of 57 to 75%.[14,15] Since phase III trials proving superior efficacy over BEP are lacking, BEP remains the mainstay of treatment.

Interestingly, 5 out of 10 hepatitis B carriers had hepatitis B flare-up with chemotherapy. Lamivudine was not routinely prescribed as prophylaxis during the study period. Currently our practice is to give prophylactic lamivudine for hepatitis B carrier patients with germ cell tumour who need to receive chemotherapy, so as to reduce the chance of hepatitis flare-up and avoid interference with the assessment of alfa-fetoprotein as a marker of treatment response.

The prognosis for stage I testicular germ cell tumour is excellent. Most patients can expect a cure and a long life expectancy. Long-term treatment toxicity is therefore a concern, and sparing patients from such toxicity becomes an issue of interest. For stage I seminoma, management options include adjuvant chemotherapy with carboplatin, adjuvant RT or surveillance; the choice depends on the risk of disease and patient's preference.[16] Adjuvant chemotherapy or RT gives a cure rate of 96%, but there are estimates that up to 88% may be overtreated, as these patients might be cured by orchidectomy alone.[17,18] Those who relapse during surveillance, however, require more intensive treatment after careful patient selection. A meta-analysis showed that patients who were on surveillance can be further classified into different risk groups according to 2 risk factors: tumour size >4 cm and rete testis invasion.[19] The 5-year relapse rate was 12% for those without any risk factor, 16% with 1 risk factor, and 32% with both risk factors. In our cohort, 75% had tumours larger than 4 cm, 2% had rete testis invasion, leaving 23% with no risk factors for which surveillance might be considered as one of the options. Of the 5 patients who did not receive adjuvant treatment, tumour sizes of the 2 relapsed patients were 10 cm and 12 cm, both of whom were successfully salvaged after BEP chemotherapy. It is difficult to draw any conclusion on the surveillance policy based on the results of this series because of the small patient numbers. In our department, a significant proportion of patients were given adjuvant treatment, as the surveillance strategy relies heavily on frequent CT scan imaging alone (as there is no representative tumour marker for seminoma) over a long follow-up duration, which poses undue resource constraint. Moreover, our patients presented relatively late with large tumours. This could be a result of patient embarrassment and delayed investigation. Further public health education may help improve awareness of this disease.

As for stage I non-seminoma, tumours with vascular invasion (16% in our cohort) is associated with about a 48% risk of relapse as opposed to 14-22% for those without vascular invasion.[20-23] Surveillance could be an option for the remaining patients as tumour markers could help detect relapses, and late relapses are not common. However, most patients in our department (95%) were treated with adjuvant chemotherapy, as a surveillance strategy demanded a stringent follow-up and imaging schedule, for which resource and compliance issues were of concern.

Regarding advanced disease, there seems to be more poor-prognosis patients in our cohort. In all, 33% and 39% of our non-seminoma patients were classified as having a good and poor prognosis, respectively, as opposed to 56% and 16%, respectively in the original IGCCCG publication.[8] Outcomes of our IGCCCG good- and intermediate-prognosis patients, with 5-year OS of 90% and 100% respectively, compared favourably with the original IGCCCG report (91% and 79%, respectively).

Indeed, we had excellent outcomes in our cohort for early germ cell tumours, as well as advanced germ cell tumours with good and intermediate prognosis that were comparable to international and previously reported local experience.[9] In contrast, outcome for those with a poor IGCCCG prognosis were less favourable, with the 5-year OS of 36% being lower than the 48% detailed in the IGCCCG report.[8] A possible explanation may be that our IGCCCG poor-prognostic patients had a worse prognostic profile. A study done by Kollmannsberger et al[24] identified prognostic subgroups among 332 patients with IGCCCG poor-prognosis germ cell cancer using cart modelling. Those with gonadal / retroperitoneal primary sites without visceral metastases were among the better group, whereas those with visceral metastases plus mediastinal primary sites were in the poor group, and the rest were in the intermediate group. Two-year survival rates of 84%, 64% and 49% were reported for the 'good-poor', 'intermediate-poor' and 'poor-poor' groups, respectively. In our study, 5 out of 7 IGCCCG poor-prognosis patients died, 2 of whom belonged to the 'intermediate-poor' and 3 belonged to the 'poor-poor' group. In addition, the number of IGCCCG poor-prognosis patients in our study was small. Any event would lead to a significant decrease in the survival estimate. Any of these factors might have resulted in a lower survival rate in our study.

Among those who had an event, 2 patients were able to achieve a relatively long (4 to 5 year) progression-free period before succumbing to the disease. Both of them had extensive resection of residual tumour after salvage chemotherapy. One patient (Patient No. 6, Table 4) had more than 95% of the lung nodules being resected. The other (Patient No. 7, Table 4) had extensive mediastinal mass resection after salvage chemotherapy and high-dose chemotherapy (HDCT), leaving only the superior vena cava thrombus behind, and pathology was reported as mature teratoma with post-chemotherapy effect. These examples illustrate the importance of aggressive surgical removal of residual masses as far as possible, so as to achieve a long-term survival.

As a means of improving outcomes in poor-prognosis patients, HDCT with autologous bone marrow transplant support has been explored in phase II single-arm studies. In our retrospective review, 4 patients received HDCT as part of the salvage treatment. Two of them had disease progression soon after HDCT and died of their disease (Patient No. 8 and 10, Table 4). One patient (Patient No. 7, Table 4) remained progression-free for 5 years after HDCT treatment, surgical resection and RT, before dying of the disease. One patient was successfully salvaged, but complete remission was already attained beforehand by VIP chemotherapy; HDCT was only given as consolidation. The outcome of our patients who received HDCT did not seem promising, though it was difficult to draw conclusions based on such a small sample. A recent multicentre randomised phase III trial of 219 patients showed that there was no statistically significant difference in 1-year durable complete response between patients receiving BEP plus HDCT versus BEP alone as first-line treatment.[25] A subset analysis of 67 patients, however, did raise the possibility that those with chemotherapy resistance (manifested by unsatisfactory tumour marker decline after 2 cycles of standard therapy) might have a higher 1-year durable complete response rate with HDCT (61% vs 34%).[25] Another prospective randomised trial comparing VIP with VIP plus HDCT after failure of first-line platinum-based treatment also did not show any survival difference.[26] Newer agents including paclitaxel, gemcitabine and oxaliplatin combinations have been tested in several studies, and seem to offer promise as salvage treatment.[27-30]

CONCLUSION

Germ cell tumour is an important cancer as it affects mainly young men and is highly curable in its early stages. Our results showed that in the local Chinese population, clinico-pathological characteristics and overall outcomes were comparable to the global experience. The outcome of the IGCCCG poor-prognosis patients remains guarded, despite salvage treatment. Multicentre collaborative research is required to further our understanding and achieve treatment breakthroughs for this disease.

REFERENCES

1. Hong Kong Cancer Statistics 2006. Hong Kong: Hong Kong Cancer Registry, Hospital Authority; 2008.
2. Peckham MJ, Barrett A, Liew KH, et al. The treatment of metastatic germ-cell testicular tumours with bleomycin, etoposide and cis-platin (BEP). Br J Cancer. 1983;47:613-9.
3. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med. 1987;316:1435-40.
4. Horwich A. Germ cell tumour chemotherapy. Br J Cancer. 1989;59:156-9.
5. Aass N, Klepp O, Cavallin Stahl E, et al. Prognostic factors in unselected patients with nonseminomatous metastatic testicular cancer: a multicenter experience. J Clin Oncol. 1991;9:818-26
6. Harding MJ, Paul J, Gillis CR, Kaye SB. Management of malignant teratoma: does referral to a specialist unit matter? Lancet.

1993;341;999-1002.
7. Collette L, Sylvester RJ, Stenning SP, et al. Impact of the treating institution on survival of patients with "poor-prognosis" metastatic nonseminoma. European Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group and the Medical Research Council Testicular Cancer Working Party. J Natl Cancer Inst. 1999;91:839-46.
8. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol. 1997;15:594-603.
9. Chan AT, Cheung MM, Lau WH, Johnson PJ. Germ cell tumours—local perspectives on a curable cancer. Hong Kong Med J. 1997;3:305-11.
10. Horwich A, Shipley J, Huddart R. Testicular germ-cell cancer. Lancet. 2006;367:754-65.
11. Fosså SD, Horwich A, Russel JM, et al. Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. J Clin Oncol. 1999;17:1146.
12. Jones WG, Fossa SD, Mead GM, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol. 2005;23:1200-8.
13. Wittes RE, Yagoda A, Silvay O, et al. Chemotherapy of germ cell tumors of the testis. I. Induction of remissions with vinblastine, actinomycin D, and bleomycin. Cancer. 1976;37:637-45.
14. Bower M, Newlands Es, Holden L, Rustin GJ, Begent RH. Treatment of men with metastatic non-seminomatous germ cell tumours with cyclical POMB/ACE chemotherapy. Ann Oncol. 1997;8:477-83.
15. Bhala N, Coleman JM, Radstone CR, et al. The management and survival of patients with advanced germ-cell tumours: improving outcome in intermediate and poor prognosis patients. Clin Oncol (R Coll Radiol). 2004;16:40-7.
16. Krege S, Beyer J, Souchon R, et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part I. Eur Urol. 2008;53:478-96.
17. Warde PR, Gospodarowicz MK, Goodman PJ, et al. Results of a policy of surveillance in stage I testicular seminoma. Int J Radiat Oncol Biol Phys. 1993;27:11-5.
18. Warde P, Gospodarowicz MK, Panzarella T, et al. Stage I testicular seminoma: results of adjuvant irradiation and surveillance. J Clin Oncol. 1995;13:2255-62.
19. Warde P, Specht L, Horwich A, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol. 2002;20:4448-52.
20. Albers P, Siener R, Kliesch S, et al. Risk factors for relapse in clinical stage I nonseminomatous germ cell tumors: results of the German Testicular Cancer Study Group Trial. J Clin Oncol. 2003;21:1505-12.
21. Read G, Stenning SP, Cullen MH, et al. Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. J Clin Oncol. 1992;10:1762-8.
22. Klepp O, Dahl O, Flodgren P, et al. Risk-adapted treatment of clinical stage 1 non-seminoma testis cancer. Eur J Cancer. 1997;33:1038-44.
23. Ondrus D, Matoska J, Belan V, Kausitz J Goncalves F, Hornák M. Prognostic factors in clinical stage I nonseminomatous germ cell testicular tumors: rationale for different risk-adapted treatment. Eur Urol. 1998;33:562-6.
24. Kollmannsberger C, Nichols C, Meisner C, Mayer F, Kanz L, Bokemeyer C. Identification of prognostic subgroups among patients with metastatic 'IGCCCG poor-prognosis' germ-cell cancer: an explorative analysis using cart modeling. Ann Oncol. 2000;11:1115-20.
25. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol. 2007;25:247-56.
26. Pico JL, Rosti G, Kramar A, et al. A randomized trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol. 2005;16:1152-9.
27. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol. 2005;23:6549-55.
28. Hinton S, Catalano P, Einhorn LH, et al. Phase II study of paclitaxel plus gemcitabine in refractory germ cell tumors (E9897): a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2002;20:1859-63.
29. Pectasides D, Pectasides M, Farmakis D, et al. Oxaliplatin and irinotecan plus granulocyte-colony stimulating factor as third-line treatment in relapsed or cisplatin-refractory germ-cell tumor patients: a phase II study. Eur Urol. 2004;46:216-21.
30. Kollmannsberger C, Beyer J, Liersch R, et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: a study of the German Testicular Cancer Study Group. J Clin Oncol. 2004;22:108-14.