REVIEW

Germ cell tumours—local perspectives on a curable cancer

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Germ cell tumours are among the most curable solid cancers and have become a model for the multimodality approach in oncology. The experience of two institutions in Hong Kong involving 149 Chinese patients with testicular germ cell tumours and 10 patients with mediastinal germ cell tumours was reviewed and the overall results were found to be comparable with the global experience. Treatment strategies suitable for the local population are discussed. The earlier identification of patients with metastatic non-seminomatous germ cell tumours who have a poor prognosis, may be important in selecting patients for more intensive treatment such as high dose chemotherapy. With mediastinal germ cell tumours, survival is poorer and improved treatment results may only be possible with increased understanding of the biological abnormalities involved. An integrated multimodality approach to the diagnosis and treatment of this disease is vital to attain optimal management. For these reasons, it is recommended that all patients with germ cell tumours be referred to cancer centres where cross-specialty expertise and experience are available to manage these patients.

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Key words: Seminoma; Teratoma; Hong Kong; Treatment outcome

Introduction

The incidence of testicular germ cell tumours (GCTs) in western populations is 3.7 per 100 000 population and represents 1% of all malignancies.[1] In Hong Kong, the reported incidence in the 1991 Cancer Registry was 0.78 per 100 000.[2]

Despite the low incidence for this disease, it is important for three reasons. Firstly, the disease is among the most common forms of malignancy found in men between the ages of 20 and 40 years. Secondly, with the development of cisplatin-based combination chemotherapy regimens and advances in surgical technique, GCT is potentially curable and has become a model for the multimodal treatment of solid malignancies. Thirdly, a better understanding of the use of serum tumour markers has allowed closer follow up of this group of patients, with earlier therapeutic intervention being possible when indicated.

This review aims to compare the local experience in the treatment of testicular GCTs with the global experience and to highlight the combined role of diagnostic radiology, radiotherapy, surgery, and medical oncology in the management of this disease. In addition to testicular GCTs, the management of mediastinal GCTs is also briefly reviewed.

Symptoms on presentation, histological classification, and clinical staging systems

The most common presentation is of a painless testicular swelling. About 10% of patients present with symptoms related to distant metastases such as neck nodes, lung metastases, or abdominal nodal metastases. Ultrasonography will confirm the presence of an intra-testicular mass and exclude the differential

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diagnoses of hydrocoele, epididymitis, orchitis, or hernia. A radical inguinal orchidectomy, with early clamping of the cord to avoid tumour seeding, removes the primary tumour and enables a pathological diagnosis to be made. The histological classification, according to WHO criteria, is generally regarded as the standard.[3] Pure seminoma is the most common GCT. The other histological types and mixed histology are collectively grouped as non-seminomatous germ cell tumours (NSGCTs) [Table 1].

The management of GCTs is guided by histological classification and clinical staging. A number of clinical staging systems have been developed for GCT of the testis. In the United Kingdom and Hong Kong, the most widely used system is the Royal Marsden Staging Classification (Table 2).[4]

Baseline investigations for all patients with GCT of the testis should include computed tomography (CT) of the thorax, abdomen, and pelvis for staging; serum tumour markers including α-fetoprotein (AFP), β-human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) for diagnosis and monitoring; complete blood picture, renal and liver function tests, and a creatinine clearance level as a baseline before nephrotoxic drugs such as cisplatin are commenced. Computed tomography has replaced lymphangiography as the standard staging investigation in GCTs. However, in some series, up to 20% of patients with negative CT findings, on retroperitoneal lymph node dissection (RPLND), have been proven to have lymph node metastases.[5] As will be discussed later, the extent of staging in NSGCT is partly determined by the institutional policy for adjuvant treatment in early stage disease.

Local experience

This review is based on the records of 149 consecutive patients with GCT of the testis who were referred to Queen Elizabeth Hospital between January 1981 through December 1992, and the Prince of Wales Hospital from February 1985 to November 1992. The patient characteristics, treatment details, and outcome of the 52 patients with NSGCT have been reported previously by Chan et al.[6] The findings are summarised below.

Table 1. Histological classification system for germ cell tumours[3]

Seminoma	
Teratoma	Mature Immature With malignant transformation
Embryonal carcinoma	
Choriocarcinoma with or without embryonal carcinoma and/or teratoma	
Yolk sac tumour (endodermal sinus tumour)	
Mixed	

Table 2. The Royal Marsden Hospital staging classification system for testicular germ cell tumours[4]

Stage		Definitions
I		No evidence of metastases
IM		Rising serum markers with no other evidence of metastases
II		Abdominal node metastases
	A	<2 cm in diameter
	B	2-5 cm in diameter
	C	>5 cm in diameter
III		Supradiaphragmatic node metastases
	M	Mediastinal
	N	Supraclavicular cervical/axillary
	O	No abdominal node metastases
	ABC	Node size defined as in Stage II
IV		Extralymphatic metastases
	Lung	
	L1	≤3 Metastases
	L2	>3 Metastases all <2 cm in diameter
	L3	>3 Metastases, one or more >2 cm in diameter
	H+	Liver metastases
	Br+	Brain metastases
	Bo+	Bone metastases

Seminoma

Ninety-seven patients had pure seminoma, of which 71 (72.4%) were stage I tumours. Following radical inguinal orchidectomy, 58 patients received radiotherapy of 30 Gy or more using inverted Y field. Twelve patients received cisplatin-based chemotherapy and one patient defaulted. The 3-year disease-free survival rate was 100% for patients with stage 1 seminoma. All patients remained alive and well at median follow up of 52 months.

Twenty-six patients (27.6%) had stage II or greater tumours. Radiotherapy was given to 10 patients. Platinum-based chemotherapy alone was given to four patients and combination chemotherapy-radiotherapy was given to eight patients. Two patients died from the disease during treatment and two defaulted treatment. As the outcomes of the latter were unknown, they were excluded from further analysis. Four patients had residual masses after chemotherapy

and resection was carried out in two of them, which yielded necrotic tissue only. Subsequently, two patients relapsed but were successfully treated with platinum-based chemotherapy. One patient developed bowel obstruction and died of this late complication of combined chemotherapy-radiotherapy two years after treatment. One patient died of a second malignancy. He was diagnosed as having histologically proven adenocarcinoma of the biliary tract, 10 years after radiotherapy. The 3-year disease-free survival rate was 83.1% for the 24 evaluable patients with stage II and above seminoma at a median follow up of 81 months. The 95% confidence interval for the Kaplan-Meier disease-free survival estimation at 3 years was 0.831 ± 0.161.

Non-seminomatous germ cell tumour

Fifty-two patients had NSGCT and 29 patients (56%) had stage I tumours. Following radical inguinal orchidectomies, two patients were offered a policy of surveillance. One patient developed lung metastases at 10 months but was successfully treated with chemotherapy and remains alive and well five years after treatment. The other patient is also alive and well. Twelve patients were given radiotherapy alone of 30 Gy or more and all remain alive and well. Eleven patients received platinum-based chemotherapy. One of these patients relapsed, refused further treatment, and died at 15 months. Four patients were given combination chemotherapy-radiotherapy and all remain alive and well. The 3-year overall survival was 96% for the patients with stage I disease at a median follow up of 49.3 months. The 95% confidence interval for the Kaplan-Meier overall survival estimation at three years was 0.960 ± 0.0377.

Twenty-three patients (44%) had stage II and greater disease. Sixteen were given platinum-based chemotherapy alone and five were given radiotherapy after chemotherapy. Of the patients with normalisation of tumour markers, four patients with residual radiological changes underwent RPLND, which revealed active disease in one patient. Figures 1a and 1b illustrate the radiological response in one of these patients. Two patients refused treatment and one died of intercurrent disease with heroin overdose during the initial treatment. Hence, these three patients were not available for response evaluations. Among the remaining 20 patients, 12 achieved complete remission and the median survival time was 87.4 months. Eight patients failed to achieve complete remission and their median survival time was seven months. The 3-year overall survival was 54% for the patients with stage II and above disease at a median follow up of 21 months.[6] The 95% confidence interval for the Kaplan-Meier overall survival estimation at three years was 0.540 ± 0.107.

Literature review and comparison with local experience

Seminoma

The majority of patients present with early stage disease (stage I, IIA, and IIB) and in this group, 90% long term survival can be expected with post-orchidectomy adjuvant radiotherapy of 30-36 Gy.[7,8]

For patients with stage IIC (tumour > 5 cm), stage III, or IV disease, the results with radiation therapy alone are unsatisfactory, with overall sur-

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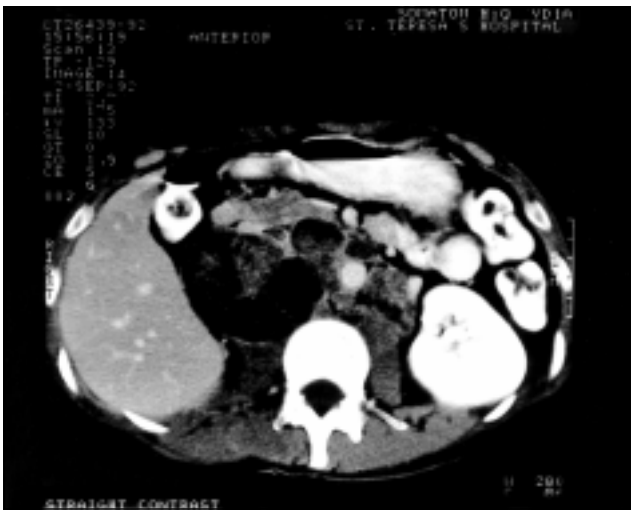

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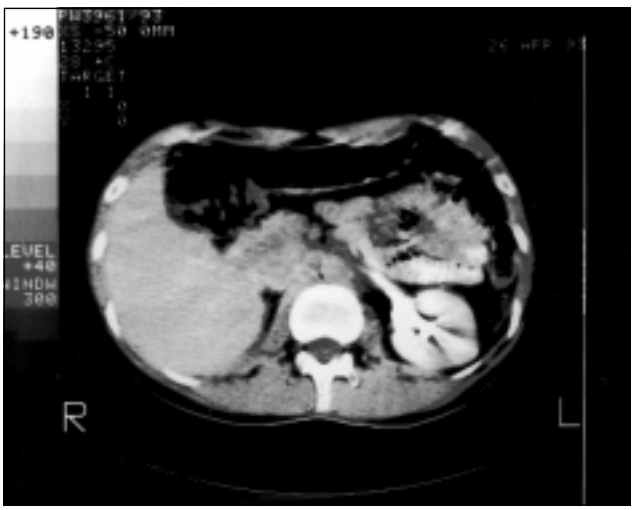

Figs 1a and 1b. Computed tomography scan appearances of a testicular non-seminomatous germ cell tumour patient before and after chemotherapy with bleomycin, etoposide, and cisplatin

vival figures of only 50% to 60%.[9,10] Several series have demonstrated superior survival rates of 80% to 90% in bulky advanced seminoma with cisplatin-based chemotherapy.[11,12] Consequently, combination chemotherapy is now considered optimal therapy for this subgroup of patients. Unlike NSGCT, the benefit of RPLND for persistent radiographic masses after chemotherapy is not proven; dense fibrosis and necrosis are the usual findings in such patients.[13,14] A series from Indiana University demonstrated encouraging results by maintaining close surveillance after chemotherapy, with salvage treatment kept in reserve for any relapse.[14]

The local and global experiences are thus similar for seminoma, with excellent survival rates for patients treated with a multimodal approach.

Non-seminomatous germ cell tumour

Management of early stage disease

With the advent of cisplatin-based chemotherapy and a better defined role for surgery, the survival rate of patients with NSGCT has improved dramatically over the past 20 years. For stage I NSGCT, the major controversy in management has been whether or not RPLND needs to be performed in order to identify the subgroup of patients who have false-negative CT results. This subgroup is reported to represent up to 30% of patients in some series. Consistent with this observation, several large scale surveillance programmes have shown a relapse rate of around 30% for NSGCT with CT stage I disease. However, salvage chemotherapy has a high success rate, and the overall mortality in these series was less than 2%.[15-17]

Retroperitoneal lymph node dissection is an extensive and technically-demanding operation with considerable associated morbidity. Prior to the modification of surgical boundaries as described by Narayan,[18] RPLND was associated with a high incidence of infertility, which was secondary to either a failure of seminal emission or retrograde ejaculation resulting from the disruption of post-ganglionic sympathetic nerve fibres that course over the aortic bifurcation to form the hypogastric plexus. Chemotherapy with bleomycin, etoposide, and cisplatin is also associated with a number of significant side effects including myelosuppression, nephrotoxicity, and pulmonary toxicity. Surveillance is thus considered a valid option to minimise the toxicities resulting from surgery or chemotherapy, provided that close supervision, frequent marker assays, and CT monitoring is available to diagnose relapse early, while it can still be treated with chemotherapy in most instances.

Despite the heterogenous approach to the treatment of stage I NSGCT in Hong Kong, the prognosis remains excellent and in line with international results. However, due to resource limitations and the frequent reluctance of the local population to be closely monitored, we recommend that all patients with stage I disease in Hong Kong should undergo treatment similar to that recommended for high risk stage I disease by a recent study—two courses of adjuvant cisplatin-based chemotherapy after a radical orchidectomy.[19]

Management of advanced disease

Prior to the development of cisplatin-based chemotherapy, the survival figures for stage II and greater metastatic NSGCT were poor. Early trials using combinations of vinblastine, dactinomycin, and bleomycin resulted in an overall survival of less than 10%.[20] Over the past two decades, cisplatin-containing regimens have dramatically improved the outcome for patients with this disease and the combination of bleomycin, etoposide, and cisplatin (BEP) has emerged as the standard regimen for treating metastatic NSGCT, with overall survival rates of 70% to 80%.[21-23]

With the increasing effectiveness of combination chemotherapy, the role of surgical management has had to be redefined. It is now generally accepted that residual masses on CT scan after four courses of BEP and the normalisation of tumour markers have to be removed by RPLND, or for other sites, by metastatectomy.[24] There remains controversy, however, on the role of surgery in patients who do not have residual abnormalities on CT scan. Since active disease has been shown to be present in up to 20% of such patients in some series,[25] the size of the initial bulk of disease has been recommended as a factor in deciding on the indication for surgery; any patient with a pre-treatment lymph node size greater than 3 cm is considered a candidate for RPLND, even if no residual abnormalities on CT are present after chemotherapy.[24] This is not universally accepted as standard practice, however, and some centres offer close surveillance for patients with no residual CT changes.

With the increasing success in the treatment of metastatic NSGCT, the identification of poor prognostic factors that may be an indication for more intensive initial therapy has become the focus of recent research.[26,27] For patients with none of the bad prognostic factors, the aim is to reduce the toxicity of chemotherapy either by reducing the number of drugs used[28] or the number of cycles given.[29] But there are no universally accepted

Table 3. Second Medical Research Council study of the prognostic factors seen in non-seminomatous germ cell tumours [27]

Adverse features
Liver/bone/brain metastases
AFP* > 1000 or βhCG† > 10 000
Mediastinal mass > 5 cm
20 or more lung metastases

* AFP α-fetoprotein

† βhCG β-chorionic gonadotropin

criteria for assigning patients into good or bad prognostic groups. In the second Medical Research Council study of prognostic factors in NSGCT, data from 795 patients were analysed and a simple prognostic classification was devised using four factors (Table 3).[27] Patients with none of the factors were put into a good prognostic group, which had a 3-year survival rate of 93%, while patients with any of the four factors were put into a poor prognostic group, with a 3-year survival of 68%. Other centres have used mathematical models to calculate the probability of a complete response.[30] Most recently, the Memorial Sloane Kettering group demonstrated the prognostic significance of the rate of fall of tumour markers during initial chemotherapy.[31] A prolonged half-life of more than seven days for AFP and more than three days for β-HCG was identified as a prognostic factor associated with a poorer outcome, although this could not be confirmed by the Royal Marsden Hospital group.[32] If patients with a poor prognosis can be identified early, when their disease is still chemosensitive, then early high dose therapy with stem cell rescue becomes a logical approach. This issue is currently being addressed by an intergroup trial in the United States, comparing high dose therapy with conventional chemotherapy in patients who have a prolonged tumour marker half life after two cycles of chemotherapy.

In the case of relapse or persistent disease after four courses of BEP, a number of salvage regimens have been developed that have achieved up to 23% disease-free survival.[33,34] Phase II studies of high dose chemotherapy using etoposide, carboplatin with or without cyclophosphamide, and stem cell rescue show that a subgroup of patients may benefit from this approach.[35,36] Until prospective randomised trials have shown a significant survival benefit, however, the use of high dose therapy for patients with relapsed NSGCT, resistant disease, or as an early treatment of disease with prolonged tumour marker half life, is not recommended outside the context of a clinical trial.

Analysis of the local experience in metastatic GCT highlights a number of factors that might account for the relatively poor survival rates. Eight patients failed to achieve complete remission with primary treatment and the outcome in this group was poor.[6] Several contributing factors were identified: delays in chemotherapy being given occurred due to myelosuppression; some patients defaulted to seek herbal treatment; carboplatin, which has been shown to be inferior in efficacy to cisplatin in NSGCT, was used[37]; delays occurred in recognising resistant or progressive disease that might have been amenable to salvage chemotherapy; and some candidates for RPLND or metastectomy were not operated on, as this option was not available at the time.

Mediastinal germ cell tumour

Extragonadal GCTs may arise from midline structures, including the mediastinum, retroperitoneum, pineal gland, thymus, stomach, or prostate. Before making a confident diagnosis of mediastinal GCT, a careful search for a testicular primary needs to be performed by bilateral testicular ultrasound. The treatment approach for mediastinal and retroperitoneal GCT is similar to testicular GCT in general, although this group of patients have a poorer survival when compared with other NSGCTs with similar bulk of disease. In the Memorial Sloane Kettering series, the median survival time for those with mediastinal NSGCT was only 12.2 months.[38] However, primary mediastinal NSGCT represents a particularly interesting biological entity with known associations with Klinefelter's syndrome and haematological malignancies.[39,40] The identification of isochromosome i (12p), which is the marker chromosome in the cytogenetic analysis of germ cell tumours[41] in a subset of acute leukaemia patients[42] suggests that the linkage of these two diseases may be a consequence of the multipotential differentiation capacity of the malignant germ cell. Apart from the association with haematological malignancies, another reason for the relatively poor prognosis may be the difficulties involved in the surgical clearance of residual disease because of the anatomical site.

Ten cases of primary GCT from the Prince of Wales Hospital between 1985 and 1994 have been reviewed.[43] Three cases with mediastinal seminoma treated with chemotherapy with or without radiotherapy were alive and well at a follow up of 8 to 42 months. Seven cases with mediastinal NSGCT were given chemotherapy

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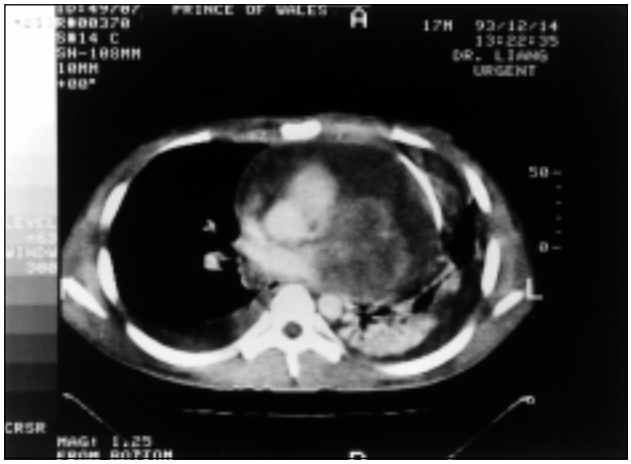

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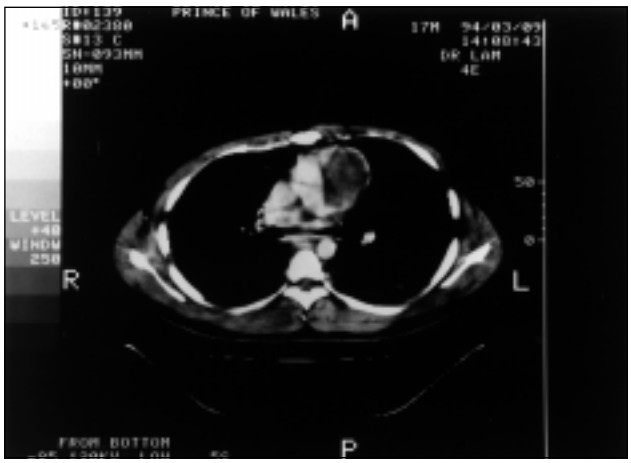

Figs 2a and 2b. Computed tomography scan appearances of a mediastinal non-seminomatous germ cell tumour patient before and after chemotherapy with bleomycin, etoposide, and cisplatin

with or without surgery. Two patients were given BEP and had normalisation of AFP levels. Both were alive and well at 12 and 16 months follow up. Figures 2a and 2b illustrate the radiological response in one of these patients. Five other patients given cisplatin-based chemotherapy failed to achieve complete remission and three died at five to nine months. One developed acute megakaryocytic leukaemia at five months and died soon afterwards. One patient had an early relapse that was resistant to chemotherapy, and also died at 18 months. Delay of chemotherapy in three of these patients was possibly a factor in their poor responses.

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