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Current Issues in Cancer

Testicular cancer and related neoplasms

G M Mead

This is the fourth in a series of articles examining recent developments in cancer.

TABLE I—Incidence of four most common cancers in men aged 15-34

Site	No of cancers/year*
Testis	485
Hodgkin's disease	255
Malignant brain tumours	155
Leukaemia	146

*Office of Population Censuses and Surveys cancer statistics registrations, England and Wales, 1985.

TABLE II—Incidence of testicular cancer in England and Wales

Year	No of cases*	Rate/100 000 population
1970	660	2.7
1975	762	3.2
1980	843	3.5
1985	922	3.8

*Office of Population Censuses and Surveys cancer statistics registrations.

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This review is primarily concerned with germ cell tumours of the testis (seminoma and teratoma), which are by far the most common testicular cancers in adults. Comparable neoplasms may, however, develop in the ovary or at extragonadal sites, particularly the mediastinum in men and the pineal area in both sexes. Primary retroperitoneal tumours probably do not occur; in such cases an occult testicular primary tumour is present.

Germ cell tumours of the testis are comparatively rare, comprising about 1% of cancers in men; however, they are by far the commonest cause of cancer in young men (table I) and their incidence has increased rapidly in the Western world,¹ as has the incidence of ovarian germ cell malignancy.

During the past 15 years management of these tumours has become highly sophisticated, and patients in whom prognosis was hopeless only 15 years ago are now commonly cured. These advances are largely due to chemotherapy, particularly with cisplatin and its derivatives.² The production of the tumour markers α fetoprotein and human chorionic gonadotrophin by these cancers is of particular importance, and they have served as a model in the search for similar markers in other tumour types.

Though most men with a germ cell tumour present with an obvious testicular mass, this is not always the case. Indeed a diagnosis of metastatic germ cell tumour needs to be excluded in any young man presenting with metastatic cancer in whom no obvious primary site is present (fig 1). This diagnosis can usually be effectively excluded by measurement of tumour markers, together with testicular ultrasonography and a review of the diagnostic biopsy specimen. No patient with a putative germ cell tumour, however ill at presentation, should be considered beyond cure. Most such patients are now managed by specialist units.

Epidemiology

In England and Wales 900-1000 new cases of testicular germ cell tumours are seen each year (representing a life time risk of about 1 in 500). There has been a remarkable 300% increase in incidence in men aged 25-29 during this century, and the numbers continue to rise (table II). The main risk factors are a history of unilateral or bilateral testicular maldescent

FIG 1—Computed tomogram of large cystic retroperitoneal mass which was the presenting feature in 33 year old man. No testicular primary tumour was palpable. Concentrations of tumour markers were greatly raised (α fetoprotein 30 300 U/l, chorionic gonadotrophin 780 U/l; normal <10). Ultrasonography showed a tumour in the right testis

(recorded in about 10% of cases of testicular cancer) or a strong family history. It is not known why testicular cancer is increasing in incidence. At present public health measures include encouraging early identification of cancers by public education and correction of maldescent (although the impact of this on the future incidence of cancer is unknown).

Pathogenesis

Testicular germ cell tumours are often histologically intimately related to areas of in situ germ cell carcinoma, and these lesions are thought to precede germ cell cancer in a high proportion of cases.³ Testicular biopsy has shown carcinoma in situ in a proportion of patients with cryptorchidism or gonadal dysgenesis and in the contralateral testis of patients with a germ cell tumour. The risk of subsequent germ cell tumour in patients with carcinoma in situ may be as high as 50%.⁴ These histological lesions can, however, be eradicated with radiotherapy.

Malignant teratoma

Malignant teratomas (or non-seminomatous germ cell tumours) comprise about 50% of testicular germ cell cancers. They occur in younger men, median age 25-30. These tumours are histologically diverse and often include various malignant and benign (teratoma differentiated) elements. In particular, recognisable areas of seminoma, trophoblastic tissue (the source of chorionic gonadotrophin), yolk sac tumour (the source of α fetoprotein), and undifferentiated elements may be present. The differentiated elements comprise mature tissues and commonly include glandular structures and cartilage. All these neoplastic elements may be present in pure form, and all are capable of metastasis.

CLINICAL MANAGEMENT

About 90% of patients with malignant teratoma have an obvious primary tumour in the testis. In the remaining cases the primary tumour may be occult (and can often be visualised by testicular ultrasonography), missed, or absent (extragonadal primary).

About 80% of patients presenting with testicular teratoma have raised concentrations of α fetoprotein or chorionic gonadotrophin, or both. Such patients should have sequential measurements of serum markers after orchidectomy together with computed tomography of the chest and abdomen. If the scan gives normal results and the concentrations of the markers fall to or remain normal the patient is regarded as having stage I disease.

STAGE I TERATOMA

Stage I teratoma comprises around 50% of cases. Traditionally these patients have been managed with radiotherapy (in Britain) or retroperitoneal lymph node dissection (in the United States). However, in recent years the accepted approach in Britain has been a "watch" policy with careful sequential review. Only 25-30% of patients managed in this fashion develop metastatic disease, usually within a year (though late relapses are well described), and almost all will be cured with combinations of chemotherapeutic drugs including cisplatin.⁵ Recent studies have focused on identifying patients at high risk of relapse by careful review of the histology of the primary tumour.⁶ Venous invasion in the primary tumour together with several other histological features have clearly been shown to be important risk factors, and trials are in progress to see if patients in these groups can be spared the risk of relapse by receiving initial limited chemotherapy.

METASTATIC DISEASE

Malignant teratoma metastasises in an unpredictable fashion. Para-aortic nodal metastases often occur first, but nodal disease in the chest and neck and lung metastases are also common at presentation. Histologically, these metastases are diverse and may contain any of the possible elements in the primary tumour.

Occasionally the presentation is fulminant, particularly when elements of choriocarcinoma predominate, when extensive lung (fig 2) and other visceral metastases are often present, commonly in conjunction with haemoptysis and gynecomastia.⁷

In Britain all patients with metastatic disease are treated with combination chemotherapy (in the United States low volume para-aortic disease is still treated surgically). Cure rates are high—in a recent Medical Research Council retrospective study 85% of patients were alive three years after treatment.⁸ Management of these patients is complex, often comprising a mixture of chemotherapy for the frankly malignant components of the disease and surgery—often multisite—for any residual masses. These commonly contain differentiated elements (which if left untreated may grow, become

FIG 2—Severe lung metastases in 33 year old man presenting with testicular mass, gynecomastia, and haemoptysis. Chorionic gonadotrophin concentration was 26 600 U/l (normal <10)

undifferentiated, or become malignant) but may also be entirely necrotic or contain active cancer.⁹

The type and intensity of chemotherapy needed is determined from known prognostic factors. In particular, bulky disease (for example, abdominal masses >10 cm, more than 20 lung metastases), disease present in the liver or central nervous system, or the presence of high marker concentrations (α fetoprotein >1000 U/l, chorionic gonadotrophin >10 000 U/l) may indicate a need for more intensive and prolonged chemotherapy treatment.⁸

The standard chemotherapy for the two thirds of cases without adverse features is bleomycin, etoposide, and cisplatin (BEP), given for four courses at three weekly intervals and followed by surgery if necessary.¹⁰ At least 90% of such patients are curable. This treatment is relatively toxic and recent trials have explored lower toxicity treatments with the aim of improving tolerance of treatment without loss of efficacy. These trials have included the use of three versus four courses of treatment,¹¹ substitution of carboplatin for cisplatin,¹² and attempts to reduce or omit the bleomycin component of the drug combination.

About 60-70% of patients with a poor prognosis are at present curable. Trials in these patients are directed at improving results of treatment, usually by using more intensive and thereby more toxic chemotherapy.^{13 14} A recent study in such patients compared standard bleomycin, etoposide, and cisplatin with a new form of this regimen containing a high dose of cisplatin.¹³ Despite increased toxicity no improvement in survival was seen. A study in Britain and Europe is currently comparing bleomycin, etoposide, and cisplatin with a more intensive treatment, BOP/VIP (bleomycin, vincristine, and cisplatin followed by etoposide, ifosfamide, and cisplatin).¹⁴ This study incorporates the haemopoietic growth factor granulocyte colony stimulating factor as part of the randomisation. It is hoped that this drug will enable more chemotherapy to be given.

Most patients with poor prognosis teratoma will require a laparotomy or thoracotomy at completion of treatment to remove residual mass lesions (fig 3).

Seminoma of the testis

Testicular seminoma comprises about 50% of cases. These cancers occur at a median age of 35-40 but may present at any point in adult life. Seminoma can

produce chorionic gonadotrophin in relatively small quantities, together with placental alkaline phosphatase. Metastatic potential is low for many of these tumours, and at presentation about 75% of men have no evidence of metastatic disease (stage I). Traditionally such patients have been treated with prophylactic radiotherapy to the ipsilateral para-aortic and pelvic lymph nodes—a well tolerated and highly successful approach for these radiosensitive tumours—with relapse rates under 5% and cure almost the rule.¹⁵ The need for radiotherapy has recently been questioned, and a few centres have adopted a watch policy, reserving treatment for relapse of disease.¹⁶ About 15% of patients in these studies have relapsed and have required chemotherapy. Relapse often occurs relatively late and sometimes at a distant site. The present consensus is that prophylactic radiation should remain the standard treatment, but current trials are assessing whether the area treated can be less extensive.

About 20% of patients with seminoma prove to have metastatic disease confined to the abdomen. Those with low volume (less than 5 cm, stages IIa and IIb) disease are conventionally treated with radiotherapy. Although rates of relapse for such patients will be higher than for those with stage I disease, cure rates remain high.¹⁷ Several groups are investigating treatment of these patients with chemotherapy (such as carboplatin), though this must be regarded as experimental at present.

Patients with more bulky disease, those relapsing after radiotherapy, or those with widespread disease at presentation are treated with chemotherapy. These patients, who are a minority, remain curable in at least 75% of cases. Current trials seek to determine the best chemotherapy regimen—the Medical Research Council is at present comparing a well tolerated treatment (single agent carboplatin)¹⁸ with a more toxic combination of cisplatin and etoposide.

At completion of treatment residual masses at the site of previous disease are common. These are probably best watched as most are benign and stabilise or resolve; surgery is difficult in this situation and residual cancer comparatively rare.

Other germ cell tumours

MEDIASTINAL AND PINEAL GERM CELL TUMOURS

Mediastinal germ cell tumours occur almost exclusively in men and pineal and suprasellar germ cell tumours in children of both sexes. Histologically these tumours mimic their testicular counterparts and both pure seminoma (known as germinoma in the central

FIG 4—Huge anterior mediastinal mass at presentation in 21 year old. No biopsy was done before treatment; his α fetoprotein concentration of 114 000 U/l was diagnostic of mediastinal teratoma

nervous system) and malignant teratoma are well described; yolk sac tumours are particularly common in the mediastinum.¹⁹

Mediastinal germ cell tumours are often far advanced at presentation (fig 4). Though seminoma is curable with chemotherapy⁷ or, for small lesions, radiotherapy, the malignant teratomas are more refractory to treatment and cure rates are lower. High dose chemotherapy is usually used together with surgery in most cases. These tumours are associated with Klinefelter's syndrome and also with various haematological abnormalities²⁰—for example, simultaneous presentation of teratoma and acute myeloid leukaemia is well described.

Pineal germinomas can be cured with radiotherapy.²¹ Pineal or suprasellar teratomas (diagnosed either by biopsy or raised α fetoprotein concentrations in the blood or cerebrospinal fluid) should be managed with chemotherapy with a substantial chance of cure.²²

OVARIAN GERM CELL TUMOURS

Ovarian seminoma (usually known as dysgerminoma) and teratoma are much less common than testicular germ cell tumours but occur in a comparably young population. These cancers can be managed in a similar fashion with a high expectation of cure—that is, combination chemotherapy containing cisplatin for metastatic disease and a watch policy (or radiation for dysgerminoma) for patients with stage I disease.²³

Follow up

Most patients with widespread germ cell cancers who achieve a complete remission remain disease free. Long term sequelae of treatment are relatively slight, fertility is often preserved, and a return to normal employment is usual.²⁴ Early relapse carries a relatively poor prognosis, though new high dose treatments may cure even patients who have been heavily treated.²⁵ Late relapse occurs in a small percentage of cases and often carries a much better prognosis.

FIG 3—Large mass of differentiated teratoma resected from the retroperitoneum of 19 year old man after chemotherapy

Conclusion

The most remarkable advance in therapeutic oncology during the past 10-15 years has been in the treatment of germ cell tumours. A high proportion of patients with these cancers are now entered into large cooperative clinical trials, which hold the key to improvements in management in the future. These tumours are diverse and their management complex; referral to specialist oncology centres with the wide range of expertise necessary to treat these fascinating neoplasms should be considered in all cases.

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Letter from Poland

Too many advisers, not enough aid

Karin Chopin

This is the first of three articles examining health issues in Poland

"The minister says you will be able to explain more easily to the English when you have seen something of our country. He would welcome the opportunity, moreover, to see for once his country through a foreigner's eyes. Would madam be interested in accompanying our itinerant minister on his travels while she is here?" Word had obviously reached the Polish deputy minister of health that someone writing for the *BMJ* was in town. I had arrived in Poland in the autumn of last year to see how the new regime was addressing the country's poor health record. Having just spent a fairly fruitless week being ushered politely from office to office, listening to a lot of rhetoric about the proposed Polish health reforms, I was most definitely interested in travels with this minister.

The quixotic and controversial deputy minister of health, government sanitary inspector, and chief environmental health officer, Zbigniew Halat MD is engaged in a personal crusade to shake the health service out of the spiritual atrophy induced by 45 years of communism. Hard working, self reliant, aggressive, and abrasively masculine, this man of Promethean energies put me in mind of a nineteenth century northern mill owner. While he attended a seemingly endless succession of meetings and conferences in horrendously smoke filled rooms all over the country I was at liberty to sit in and listen, or privileged to roam free throughout hospitals, talking to patients and staff, or honoured as a foreign guest in schools, academic

institutions, and factories. Over the next three months I was shown such a picture of Poland that I felt I had been to the horizon and back. Miraculously, door after door opened before me. I was profoundly touched by the warm acceptance and generosity with which I was received everywhere I visited, deeply appreciated after the struggle of Poland's paradoxical public boorishness. For all the traumas of their recent past, the Poles have retained their legendary hospitality, sense of humour, and capacity for enjoyment.

HIV and the church

My first expedition with Minister Halat was to a rehabilitation centre for HIV positive drug misusers just outside Warsaw, run by Father Arkadiusz Nowak, one of the angriest of the many angry citizens I met while I was in Poland. He is enraged by the attitude of the church on HIV: the Polish Primate, Cardinal Glemp, had just refused to sanction his request that he be allowed to issue condoms to a young couple who had recently come to live at the centre, and of whom only one was HIV positive; or, indeed, to allow him to give confession to members of the gay community, arguing that this would be tantamount to "encouraging them in their sinful ways." This newly set up centre had been receiving a great deal of media attention, since its residents had become a target for bigotry and violence from certain local factions; the minister was calling in

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