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Does Extragonadal Presentation Impart a Worse Prognosis to Abdominal Germ-cell Tumours?

James J.A. McAleer, Judy Nicholls and Alan Horwich

The prognostic significance of extragonadal rather than gonadal presentation of germ-cell tumour in 51 patients presenting between 1979 and 1988 with abdominal tumours was compared with that of 51 control patients with testicular primary tumours matched for bulk of disease, serum tumour marker concentration, age and year of treatment. Very large volume tumour was found at initial staging in 24 extra-gonadal cases (47%) and high tumour markers in 29 (57%). Actuarial survival at 2 and 5 years was 82% and 70% for cases and 78% and 63%, respectively, for controls. These outcomes were not significantly different and the relative hazard of death for cases compared with controls was 0.7 (95% confidence intervals 0.3–1.5). Thus the presentation of germ-cell tumours with a retroperitoneal mass does not itself adversely influence prognosis compared with testicular presentation with equivalent disease extent. However it is rare for extragonadal presentation to be associated with small volume disease.
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INTRODUCTION

APPROXIMATELY 5–10% of male patients with germ-cell tumours present without an overt testicular primary [1]. These presentations are termed "extragonadal" although in some cases they may arise from a small occult testicular primary tumour. It has been suggested that extragonadal presentation is associated with a poor prognosis [2, 3] and in the classifications used by the Memorial Sloan Kettering Cancer Center and by the National Cancer Institute all such patients are classified as having an adverse prognosis regardless of other features of their illness [4]. However, the lack of early symptoms with extragonadal presentation gives rise to a pattern of bulkier and more advanced disease at presentation than with testicular primary tumour and may account for the perception that the prognosis is worse. We have therefore compared the prognosis of patients with extragonadal germ-cell tumour (EGCT) to that of matched controls presenting with a testicular primary tumour to determine if extragonadal presentation is an independent indicator of poor prognosis, or merely linked to extent of metastatic disease.

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PATIENTS AND METHODS

Patient selection

Patients selected for this study were diagnosed in the years 1979 to 1988 inclusive and met the following criteria: diagnosis of germ-cell malignancy (histology or raised serum levels of alphafetoprotein (AFP) or beta sub-unit of human chorionic gonadotropin (HCG); and both testes present in scrotum without palpable testicular tumour. Patients with disease limited to the mediastinum or pineal area were excluded as there were inadequate numbers of matched controls. 51 patients fulfilled

the above criteria. Staging was based on the Royal Marsden classification [5] and investigations included clinical examination, chest radiography, computed tomography (CT) scans of chest and abdomen and pretreatment serum AFP and HCG. 14 patients (27%) presented with stage II disease, 7 (14%) with stage III and 30 (59%) with stage IV disease. Using the 1985 Medical Research Council criteria [6], 24 (47%) had very large volume disease, including 17 with L3 lung disease, 8 with liver involvement, 4 with bony involvement and one with brain disease. Histological diagnosis was obtained by laparotomy in 22 cases, by needle biopsy of an abdominal mass in 5 cases and by lymph-node biopsy in 11. For 6 patients no positive histology was obtained before treatment.

Treatment in all cases included "platinum"-based chemotherapy, with the exact regime determined by contemporary institutional policy. Bleomycin, etoposide and cisplatin or carboplatin [7] was used in 19 patients; bleomycin, vinblastine and cisplatin (PVB) was used in 12 cases. A weekly intensive induction regime of bleomycin, vinblastine and cisplatin [8] was used in 7 cases, and 6 patients with pure seminoma received single agent carboplatin [9]. A further 7 patients received other regimes.

Following chemotherapy for non-seminomatous tumour a residual abdominal mass was removed from 23 patients and a chest mass from 4. Undifferentiated tumour was found in 5 cases and differentiated teratoma in 8 cases.

Selection of matched controls

Controls were drawn from the Royal Marsden Testicular Tumour Database, having excluded patients with stage 1 disease, extragonadal primary or second primary tumour. For each case one control was randomly and anonymously selected from all records which met the following criteria: year of treatment: within 1 year; age: < 30 years, > 30 years; tumour markers: low or high (AFP > 500 ng/ml or HCG > 1000 U/l); tumour volume: small, large, very large volume.

Basis of comparison

Distribution of ages, AFP and HCG and duration of follow-up for cases and controls were compared using Wilcoxon's matched-pairs signed-ranks test [10]. Histological findings at diagnosis and Royal Marsden staging were compared using the χ^2 test. McNemar's test [10] was used to compare the number of cases and controls with raised AFP or HCG and the number with involvement of bone brain and liver at presentation. The Mann–Whitney U test [10] was used to compare duration of follow-up.

A matched-pairs analysis [11] was used to compare the survival in cases and controls and to estimate the hazard of death in cases relative to controls.

RESULTS

Comparison of cases and controls

There were 51 pairs in this study and the distributions of prognostic variables in cases and controls were compared to assess the adequacy of the matching process. Data for age, serum AFP, serum HCG levels and histological classification are shown in Table 1. Serum AFP levels tended to be higher in controls, although the numbers with raised AFP (16 cases compared with 19 controls) was not significantly different.

There were equal numbers of cases and controls with pure seminoma (13, 26%). The histological categories malignant teratoma trophoblastic (MTT) and malignant teratoma undifferentiated (MTU) were more common in cases than in controls, whereas there were more diagnoses of malignant teratoma intermediate (MTI) and mixed tumours in control patients; none of these differences was statistically significant. The comparison of cases and controls by Royal Marsden Hospital stages and by involvement of bone, brain and liver at presentation (Table 2), revealed no significant differences.

Table 1. Comparison of age, tumour markers and histology for cases and controls

	Cases	Controls	*P* value
Age: Median (range)	30 (16–64)	31 (16–51)	0.6
AFP: Median	10	90	0.12
Values > 500	16	19	0.28
HCG: Median	80	95	0.9
Values > 1000	18	18	0.8
Histology			
Seminoma	13	13	
MTI	4	14	
MTU	16	9	
MTT	9	5	
TD	0	1	
Mixed tumour	1	6	
Not defined/none	8	3	
Total	51	51	0.08

AFP, alphafetoprotein; HCG, beta-sub-unit human chorionic gonadotrophin; MTI, malignant teratoma intermediate; MTU, malignant teratoma undifferentiated; MTT, malignant teratoma trophoblastic; TD, teratoma differentiated.

Comparison of outcome

All patients had been treated before January 1988 and survival was analysed at 31 January 1989; thus all patients had been followed up for at least 13 months. Median duration of follow-up for surviving patients was not significantly different ($P = 0.48$), being 64 months (range 8–125) for cases and 58 months (3–120) for controls. Actuarial survival at 2 and 5 years was 82% and 70% for cases and 78% and 63% for controls (Fig. 1). The survival experience for cases and controls did not differ significantly ($P = 0.42$). The relative hazard of death for cases compared to controls was 0.7 (95% confidence limits 0.3–1.5).

Table 2. Comparison of Royal Marsden Hospital Stage and involvement of liver, brain and bone at presentation for cases and controls

	Cases	Controls	*P* value
Stage II	14	18	
Stage III	7	3	
Stage IV	30	30	0.35
Involved sites			
Liver	8	6	0.72
Brain	1	4	0.25
Bone	4	2	0.68

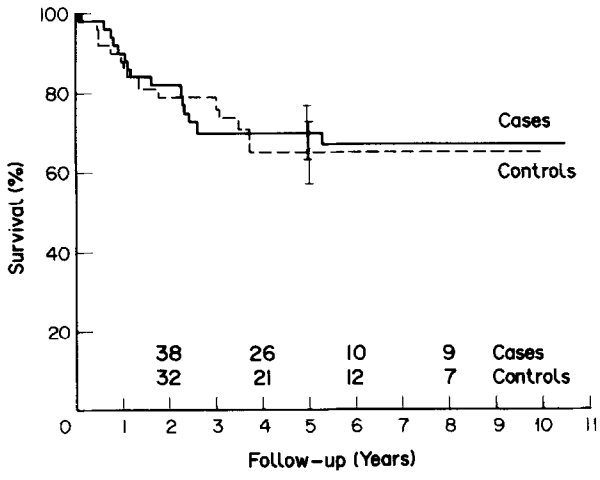

Fig. 1. Actuarial survival of patients with extra-gonadal germ cell tumour (cases) and matched patients with testicular primary (controls). The numbers of patients remaining in the study at 2-year intervals are indicated above the *x*-axis and the error bars are mean (1 S.E.).

Patients with a histological diagnosis of seminoma had a good prognosis. 1 of 13 cases died, giving an actuarial survival of 90%. There were no deaths in the corresponding controls. However the "seminoma" patients also had less advanced disease with only 2/13 (15%) having very large volume disease compared to 22/38 (58%) of those with other histological diagnoses.

DISCUSSION

The development of effective platinum-based chemotherapy has resulted in a marked improvement in the disease-free survival rate for metastatic germ-cell tumours and, with experience and refinement of these regimes, outcome has further improved [12]. Reports on EGCT treated with platinum-based chemotherapy are generally less optimistic. This may be due to the small size of most reported series and differences in inclusion criteria and treatment protocols.

In setting entry criteria for this study we defined EGCT using the straightforward clinical presentation of metastatic germ-cell tumour with normal clinical findings on scrotal examination. Some patients in this group 25/51 (48%) subsequently showed evidence of testicular abnormality, and underwent surgical evaluation. Abnormal histological findings included differentiated teratoma in 4 cases, undifferentiated teratoma in 5 cases and scarring in 7 patients. Postmortem examination of the testes on a further 3 patients dying of extensive disease yielded 1 case with differentiated teratoma. 8 patients had described episodes of significant testicular pain prior to presentation and testicular atrophy was noted at presentation in 12 cases. The above findings confirm that some EGCT patients have occult primary testicular tumour [13–15]but in this series almost half the patients did not have testicular surgery and of those having surgery only 10/26 (39%) had tumour identified. The histological finding of scarring is often regarded as evidence of regressed primary tumour but some authors question this interpretation [16].

Germ-cell tumours arising in the mediastinum and pineal areas were excluded from this study as they have a distinct clinical site of involvement and thus controls with a testicular primary would be rare. The 51 cases reported together with 21 excluded (17 mediastinum, 4 pineal) constituted 8% (72/948) of the patients presenting with germ-cell tumours over this period. Hitchins *et al.* [17] reported that all extra-gonadal presentations accounted for 11% of their germ-cell tumour patients. Since both centres are specialist referral centres the underlying incidence of extra-gonadal presentation may be considerably less [18]. Since extragonadal presentation of germ-cell tumour is relatively infrequent, reported series on EGCT tend to have small numbers of cases. In reviewing other series patients with mediastinal primary tumour are excluded to allow a direct comparison with this study.

Logothetis *et al.* [19] reported on 56 patients of whom 37 were comparable with our study group. Of 7 patients treated with a chemotherapy regime which did not contain platinum only 1 remained disease free. Of 30 patients receiving platinum-based chemotherapy 19 (63%) were in complete remission. The authors concluded that PVB chemotherapy was satisfactory for these patients.

Hainsworth *et al.* [20], using PVB, achieved an actuarial 5 year survival of 64% for 31 evaluable patients, including mediastinal primary, with the exact outcome of the 15 patients comparable to our study not being delineated separately. These authors concluded that the poor prognosis of EGCT was related to the advanced disease and not to the extra-gonadal presentation.

Israel *et al.* [3] reported durable complete response in 15 of 38 patients of whom 22 had mediastinal primary site, but the breakdown of outcome by site was not given. In other series reporting less than 10 comparable cases [2, 21–24] results were variable: less than 50% of patients achieved disease-free survival with better outcome occurring in the larger series. Several reports discuss the possible importance of the advanced disease at presentation as an explanation of the poor prognosis of EGCT [20, 25]. Our study design has allowed analysis of control patients with testicular primaries matched for known prognostic variables including age, tumour bulk and serum tumour marker levels [6]. They were treated contemporaneously using the same treatment guidelines for both groups and treatment outcome was broadly similar, as demonstrated by the survival curves (Fig. 1). We recommend that patients with an abdominal extra-gonadal presentation of germ-cell tumour should be accorded the treatment regime considered appropriate for similar disease with a testicular primary tumour, with the expectation of a similar outcome.

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Quantification and Molecular Analysis of Cathepsin D in Breast Cyst Fluids

Luis M. Sánchez, Francisco Vizoso, M. Teresa Allende, Alvaro Ruibal and Carlos López-Otín

Cyst fluids from 55 premenopausal women with gross cystic breast disease were classified by K^+/Na^+ ratio: 19 with ratio over 1 (type I) and 36 with ratio less than 1 (type II). Immunoradiometric assay of cathepsin D in both types of cyst fluids revealed the presence of large amounts of this proteinase. The average concentration of cathepsin D in type I cyst fluids was 63.3 nmol/l, which was significantly higher than that corresponding to type II cyst fluids (35.1 nmol/l). Immunoprecipitation analysis of intracystic cathepsin D demonstrated that this protein was present as the 52 kD non-processed precursor form of the molecule. Since procathepsin D is a useful prognostic marker in breast carcinoma, we suggest that cyst fluid quantification of cathepsin D could aid to detect patients affecting of gross cystic disease with higher risk for developing breast cancer.
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INTRODUCTION

GROSS CYSTIC breast disease is the most common mammary pathology in premenopausal women, affecting about 7% of women in Western populations [1]. Although the relationship of gross cystic disease to breast carcinoma is controversial [2], there is statistical evidence indicating that patients with gross cystic lesions are at a 2–4-fold greater risk of developing breast cancer than the normal female population [3, 4].

The biochemical composition of cyst fluid aspirated from patients with gross cystic breast disease has been studied in an attempt to understand the mechanisms involved in cyst formation and to define their possible role in carcinogenesis. These analyses have demonstrated that cyst fluids contain a wide variety of substances at concentrations more than 100 times higher than the levels found in plasma. These substances include conjugated steroids [5, 6], tumour markers [7, 8], epidermal growth factor [9, 10] and several unusual proteins that seem to be specific secretory products of epithelial cells surrounding the cysts [11–13].

In addition, analyses of the composition of fluid filling the cysts have allowed cysts to be typed into two principal categories according to the concentrations of different intracystic sub-