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TUMOUR-MARKER LEVELS AND PROGNOSIS IN MALIGNANT TERATOMA OF THE TESTIS

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Summary.—The effect of 6 putative prognostic factors on survival was studied in patients with Stages III and IV malignant teratoma of the testis. Differences between survival curves were tested for statistical significance. A diameter >5 cm in the largest tumour mass, and >8 pulmonary metastases were adverse prognostic factors ($P=0.004$ and 0·008 respectively). Patients with malignant teratoma, trophoblastic, fared worse than those with malignant teratoma, undifferentiated, and malignant teratoma, intermediate ($P=0.011$ and 0·023 respectively). Previous chemotherapy or radiotherapy had no significant effect.

Serum α-foetoprotein (AFP) above 10^3 MRC u/ml and serum β subunit of human chorionic gonadotrophin (hCG) above 10^5 miu/ml, were found to predict a poor prognosis ($P=0.010$ and 0·001 respectively). A combination of measurements of the tumour markers gave the most consistent indication of prognosis, in that patients with either AFP $>10^3$ MRC u/ml or hCG $>10^5$ miu/ml, or both, fared much worse than those with neither factor ($P=0.001$).

Serum concentrations of AFP and hCG should be stated in reports of treatment of testicular teratoma in order to provide a basis for comparison with other series. Regular and frequent measurements of these markers are appropriate throughout the clinical management of patients with malignant teratoma.

SINCE THE INTRODUCTION of combination chemotherapy for advanced metastatic testicular teratoma in the 1960s, there has been a progressive improvement in the long-term disease-free survival (MacKenzie, 1966; Jacobs *et al.*, 1979). Improved chemotherapy regimens including vinblastine and bleomycin (Samuels *et al.*, 1976) and, more recently, *cis*-platinum (Golbey *et al.*, 1979; Einhorn & Donohue, 1979; Newlands *et al.*, 1980) have produced disease-free survival of more than 2 years in 30–74% of patients. It would be advantageous to be able to predict which patients are unlikely to achieve full remission with present therapy.

The relationship of tumour bulk to prognosis is widely recognized (Samuels *et al.*, 1976; Einhorn & Donohue, 1977; Peckham *et al.*, 1977) but tumour bulk, as estimated by a variety of methods, is not readily quantified. Studies of putative prognostic factors related to tumour bulk are reported in this paper.

Human chorionic gonadotrophin (hCG) and α-foetoprotein (AFP) are found separately or together in the serum of more than 75% of patients with disseminated malignant teratoma (Newlands *et al.*, 1976; Javadpour, 1979). Changes in the concentration of these markers in serum are usually related to the bulk of tumour in an individual patient (Javadpour, 1979). The proportion of patients with hCG or AFP detectable in the serum is higher in metastatic than in localized

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disease (Schultz *et al.*, 1978). Although not all cells in malignant teratomas secrete these markers, it is possible that their serum concentrations can be related to overall tumour bulk and, on the evidence presented here, can provide the most consistent indication of prognosis.

METHODS

Forty-seven patients with malignant teratoma of the testis Stages III (5) and IV (42) (Smithers & Wallace, 1962) began treatment between August 1975 and March 1979. Ages were 16–45 years (mean and median 27). The criteria of Pugh & Cameron (1976) were used for histological classification.

The largest tumour diameter was determined by clinical measurement, plain radiography of the chest, bipedal lymphangiography or computerized tomography of the chest or abdomen. Assays for the β subunit of hCG used the method of Kardana & Bagshawe (1976) and for AFP the method of Seppälä & Ruoslahti (1972) automated as described by Bagshawe (1975).

All patients received cytotoxic chemotherapy, surgery and radiotherapy being used where appropriate. From August 1975 to April 1977, multiple cytotoxic drug regimens were being developed, based on combinations of vincristine, methotrexate with folinic acid rescue, cyclophosphamide, bleomycin, actinomycin D and adriamycin. From April 1977 a regimen comprising vincristine, methotrexate, bleomycin and high-dose *cis*-platinum was given for the 2 courses, followed by courses of VP 16-213, actinomycin D and cyclophosphamide alternating with hydroxyurea, vinblastine and chlorambucil, and vincristine, methotrexate and bleomycin (for details see Newlands *et al.*, 1980). The rate of accrual of patients in various prognostic groups was approximately constant throughout the study.

Life tables were constructed using the Statistical Package for the Social Sciences Program for Survival Analysis, Version 7.0 (Nie *et al.*, 1977) in which differences in the survival curves were tested for statistical significance by a non-parametric technique described by Lee & Desu (1972). Data were processed by these programs at the University of London Computer Centre, *via* the Charing Cross Hospital Medical School Computer Unit.

RESULTS

Forty-seven consecutive patients starting treatment between August 1975 and March 1979 were investigated for survival up to June 1980. The 6 putative prognostic factors studied at the start of chemotherapy were: (1) largest tumour mass at any site >5 cm diameter; (2) more than 8 lung metastases; (3) previous chemotherapy or radiotherapy; (4) histological type; (5) serum concentration of AFP and (6) serum concentration of hCG. An adverse prognostic factor is defined for this purpose as an indicator, determined at the start of therapy, and associated with a low probability of survival. This was determined by finding a statistically significant difference between survival curves for groups of patients with or without the indicator.

Tumour bulk and number of pulmonary metastases

Figs 1 and 2 show that a diameter >5 cm in a tumour mass at any site, or

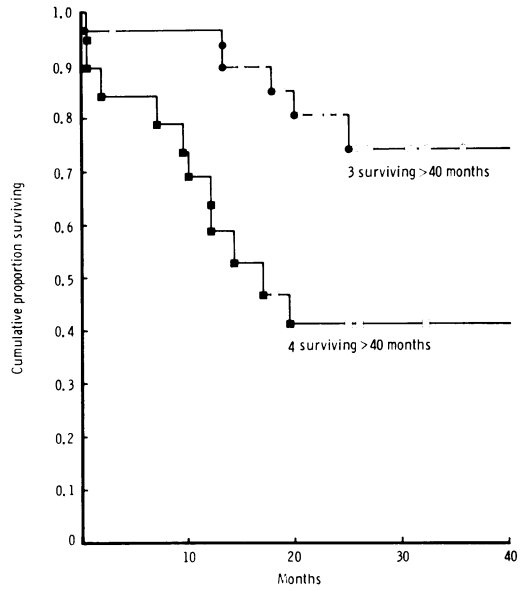

FIG. 1.—Life tables for groups with largest tumour mass with a diameter above (19 patients) (■ dead, □ alive) or below 5 cm (28 patients) (● dead, ○ alive). $P=0{\cdot}004$.

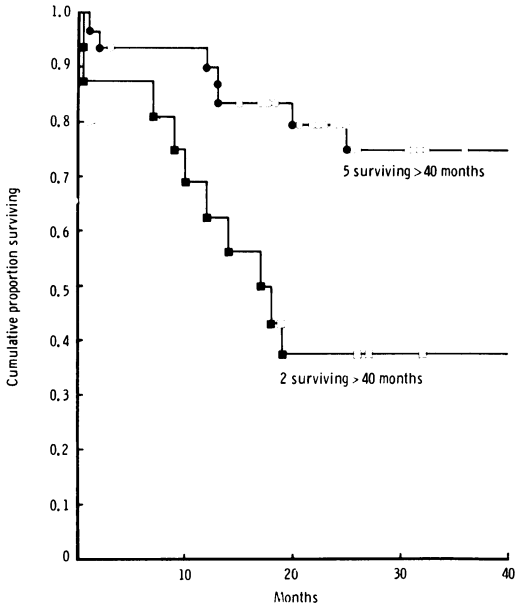

FIG. 2.—Life tables for groups with pulmonary metastases numbering 8 or less (31 patients) (● dead, ○ alive) or more than 8 (16 patients) (■ dead, □ alive) on a plain radiograph. $P = 0{\cdot}008$.

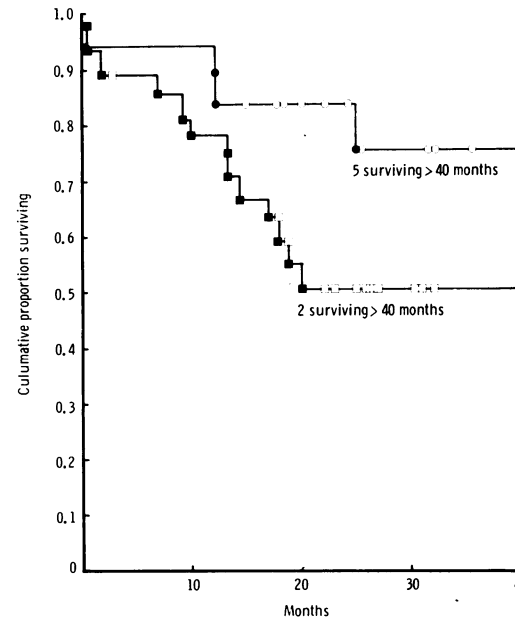

FIG. 3.—Life tables for groups with (19 patients) (● dead, ○ alive) or without previous chemotherapy or radiotherapy (28 patients) (■ dead, □ alive). $P = 0{\cdot}079$.

the presence of > 8 lung metastases, were adverse prognostic factors ($\chi^2 = 8{\cdot}08$, d.f. $= 1$, $P = 0{\cdot}004$ and $\chi^2 = 7{\cdot}14$, $P = 0{\cdot}008$ respectively).

Previous treatment

Patients who had received previous chemotherapy or radiotherapy fared better than those without previous treatment, but the difference did not reach statistical significance ($\chi^2 = 3{\cdot}08, P = 0{\cdot}079$) (Fig. 3). It was found that 76% of previously untreated patients had one or more of the 4 adverse prognostic factors related to tumour bulk, compared with only 48% in the previously treated group.

Histological type

Patients with malignant teratoma, trophoblastic, fared significantly worse than the other two groups (Fig. 4); $\chi^2 = 6{\cdot}45$, $P = 0{\cdot}011$ for the comparison with malignant teratoma, undifferentiated, and $\chi^2 = 5{\cdot}16$, $P = 0{\cdot}023$ for the comparison with malignant teratoma, intermediate.

AFP

Fig. 5 shows that AFP $> 10^3$ MRC u/ml (1 MRC u/ml = 1 μg/l) immediately before starting chemotherapy, is associated with a relatively poor prognosis ($\chi^2 = 6{\cdot}67$, $P = 0{\cdot}010$). AFP $> 5 \times 10^2$ MRC u/ml had no significant effect on survival ($\chi^2 = 1{\cdot}165$, $P = 0{\cdot}200$) when investigated by the same method (data not shown).

hCG

Fig. 6 shows that hCG $> 10^5$ miu/ml is associated with a poor prognosis ($\chi^2 = 12{\cdot}18$, $P = 0{\cdot}001$). A significant but less marked difference was also found between hCG above and below 5×10^4 miu/ml ($\chi^2 = 6{\cdot}89$, $P = 0{\cdot}009$; data not shown).

Tumour markers in combination

The most consistent indication of prognosis was given by combination of measurements of both tumour markers: patients with neither AFP $> 10^3$ MRC u/ml, nor hCG $> 10^5$ miu/ml, fared significantly

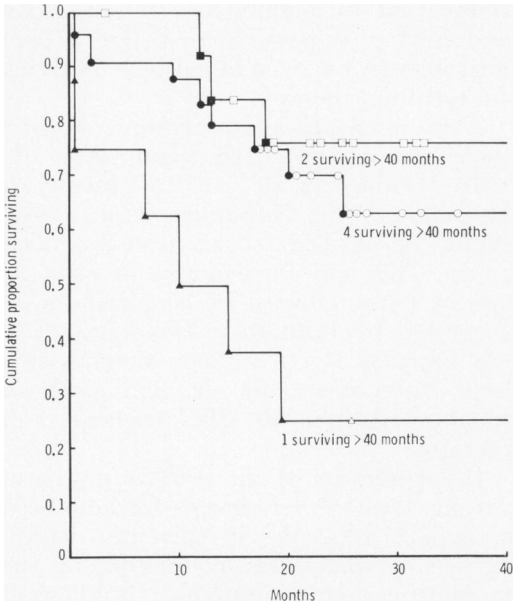

FIG. 4.—Life tables for groups with tumours in the 3 histological categories: MTU = malignant teratoma undifferentiated (15 patients) (squares); MTI = malignant teratoma intermediate (24 patients) (circles); MTT = malignant teratoma trophoblastic (8 patients) (triangles). Open symbols, alive; closed symbols, dead.

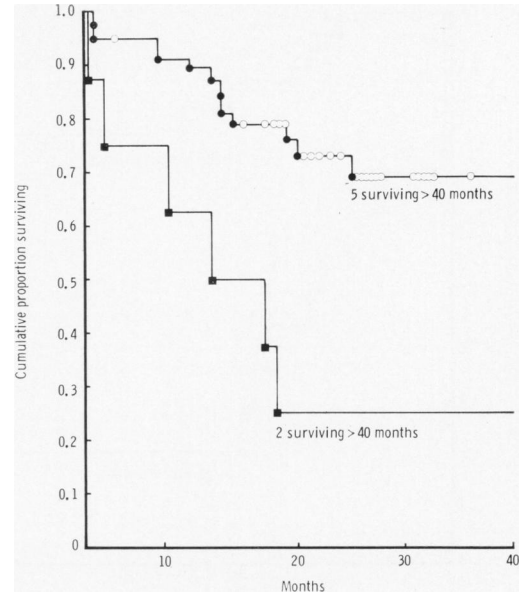

FIG. 5.—Life tables for groups with serum AFP above (8 patients) (squares) and below 10^3 MRC u/ml (39 patients) (circles). $P = 0{\cdot}01$.

better than those with either or both factors ($\chi^2 = 17{\cdot}79$, $P = 0{\cdot}001$; Fig. 7).

DISCUSSION

The results show that serum concentrations of AFP $> 10^3$ MRC u/ml and hCG $> 10^5$ miu/ml predict poor survival in patients with malignant teratoma of the testis. A large bulk of tumour at the start of treatment also predicts poor prognosis, but high concentrations of the tumour markers appear to give a more accurate indication of the outcome, producing the highest χ^2 (17·79) when used in combination. This may be because they reflect the number of tumour cells more accurately than the relatively crude methods for physical assessment of tumour bulk which cannot assess the viable tumour fraction within a mass.

Whilst hCG and AFP are produced by trophoblastic and yolk-sac elements of the

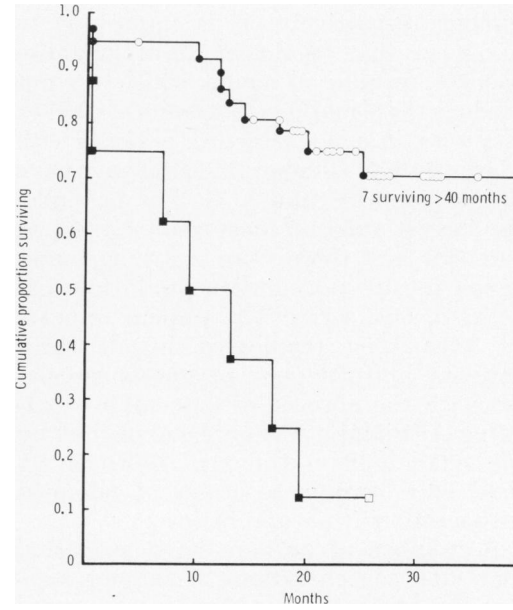

FIG. 6.—Life tables for groups of patients with serum hCG above (8 patients) (squares) and below 10^5 miu/ml (39 patients) (circles). $P = 0{\cdot}001$.

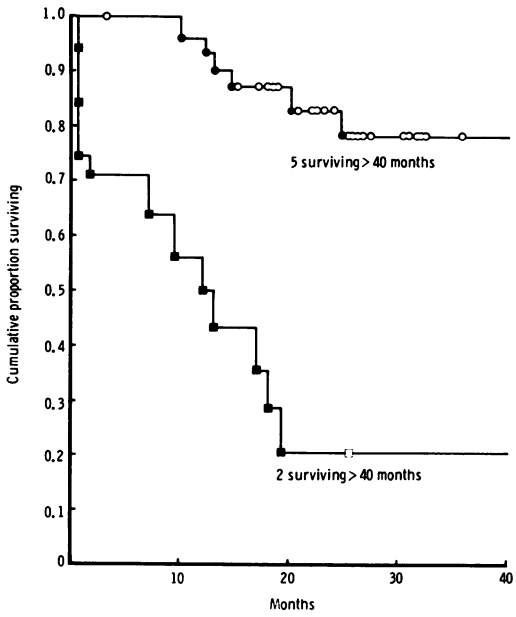

FIG. 7.—Life tables for groups of patients with neither serum AFP above 10^3 MRC u/ml nor serum hCG above 10^5 miu/ml (33 patients) (circles) and those with one or both of these factors (14 patients) (squares). $P = 0{\cdot}001$.

tumour respectively, it is important to recognize that testicular teratomas frequently contain elements which do not produce these markers (Kuram *et al.*, 1977). However, in our experience, patients with a large bulk of tumour almost always have circulating AFP and hCG. For example, the largest tumour mass was < 5 cm in diameter and there were < 8 lung metastases in 6/7 non-marker-producing patients in this series. The tumour appears to have been eradicated in all these patients, and the good prognosis associated with the absence of detectable circulating AFP and hCG may be explained by the small bulk of tumour. Alternatively they may contain a group of tumours with a different natural history.

A number of authors have suggested that high concentrations of tumour markers might be associated with poor prognosis (Einhorn & Donohue, 1977; Storer *et al.*, 1979; Golbey *et al.*, 1979). Our evidence supports this contention, and shows that by making use of both AFP and hCG it is possible to define a poor prognosis group, even in patients receiving *cis*-platinum therapy.

New approaches to therapy beyond those recently reported (Samuels *et al.*, 1976; Golbey *et al.*, 1979; Einhorn & Donohue, 1979; Newlands *et al.*, 1980) should be applied to this poor-prognosis group. This may for example involve the use of extra courses of *cis*-platinum as suggested by Einhorn & Donohue (1979) and Storer *et al.* (1979) for patients with a large bulk of tumour or high levels of tumour markers at the beginning of therapy.

Interpretation of the relative merits of various treatment regimens for advanced malignant teratoma is currently handicapped by difficulties in determining the prognostic factors applying to different groups of patients. Physical measurement of tumour bulk is of considerable help, but differences in measurements by individual observers using various diagnostic tools mean that comparisons between centres are often invalid. Assays for hCG and AFP using internationally accepted standards have the potential to overcome this problem, and it is suggested that serum hCG and AFP data for each patient at the start of treatment should be stated in reports of therapeutic trials in malignant teratoma.

The recognition of the grave prognostic significance of high levels of hCG and AFP is likely to be of most benefit to patients with testicular teratoma if assays are done regularly from the earliest suspicion of the diagnosis, as recommended by the International Research Group for Carcinoembryonic Proteins (Nørgaard-Pederson *et al.*, 1978). In our view, measurements should also be made monthly for at least 5 years after the patients are apparently free from disease by all parameters. In this way it will usually be possible to detect early relapse and re-start appropriate treatment at a stage when current methods of therapy already give a good prognosis.

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