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Carcinoma of the Prostate: Relationship of Pre-treatment Hormone Levels to Survival

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Abstract—*Pretreatment hormone levels were determined in 222 patients with prostatic cancer and their prognostic value assessed. The patients were grouped into yearly survival categories and only those whose cause of death was due to the disease were included in the study. Low concentrations of testosterone in plasma at the time of diagnosis related to a poor prognosis. Patients who died within 1 yr of diagnosis had the lowest mean plasma levels of this steroid. The pretreatment mean plasma testosterone concentrations were found to be higher as the survival period of the various groups lengthened. This relationship was observed both when the total data were analysed and also when the patients were subgrouped depending on clinical evidence of spread of the tumour beyond the prostatic capsule (T3) or on the presence of metastases (M1). High pretreatment plasma concentrations of luteinizing hormone were also associated with poor survival. Follicle-stimulating hormone, prolactin and growth hormone concentrations did not correlate with survival time. The indications from this study are that poor testicular function is associated with early death from prostatic carcinoma and that the measurement of blood levels of testosterone at diagnosis could provide a prognosis of subsequent life-span.*

INTRODUCTION

AN ABNORMAL hormonal status in the aetiology of prostatic carcinoma is still being sought. It has long been accepted that the disease occurs at a time of waning testicular function and yet, in the main, is considered androgen-dependent. Considerable research has been undertaken in an attempt to identify any endocrine abnormalities that might relate to the onset and promotion of prostatic cancer [1–3]. The results have indicated that there are no significant differences in circulating plasma androgens, oestrogens or pituitary hormones in patients with prostatic cancer or with benign prostatic hyperplasia, or in age-matched asymptomatic control subjects [3–5]. It has been shown, however, that changes occur in plasma hormone concentrations in men with prostatic cancer that can be related to the clinical stage of the disease [6], tumour grade [7, 8] and primary clinical response [9], indicating a hormonal influence on tumour development.

The life-expectancy of men with prostatic cancer is variable, and the prognostic factors involved not fully known. This study has been aimed at evaluating the functional activity of the pituitary–testicular axis at the time of initial diagnosis of the disease in relation to subsequent life-span.

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MATERIALS

Patients

This study involves 222 patients with prostatic cancer, aged between 53 and 85 yr, who had presented at one of the clinics associated with the British Prostate Group and had been classified and assessed according to a standardised protocol accepted by the group [6]. All the patients had histologically proven carcinoma of the prostate and had not previously received any therapy for their disease. They were classified according to primary tumour stage and metastatic status, using the T and M categories recommended by the UICC [10]. The patients all received endocrine therapy as the primary treatment, the majority receiving diethylstilboestrol (1 mg t.d.s.), others being orchidectomized and a few being given either ethynyl oestradiol (50 μg t.d.s.) or Honvan (100 μg b.d.). The survival groups were comparable in terms of initial therapy, the proportions of given oestrogen as treatment to orchid-

ectomized patients being very similar in each group. Secondary treatment was more varied but the majority of patients remained on their primary therapy. Initial treatment was around 1-2 weeks after diagnosis. Only individuals whose cause of death was primarily related to prostatic cancer were included in the analysis. The total patient population under study is over 600 individuals, but this communication does not include those patients who died from cardiovascular diseases or other diseases, or those patients whose cause of death was unknown. Neither does it include those patients in which treatment was deferred or patients who received radiotherapy as their primary treatment. Patients who were alive 3 yr or more after initial diagnosis were included in the study, whereas those patients who are still alive but have only been in the study for under 3 yr were excluded.

Before institution of therapy, blood samples were taken, as near as possible to 09.00hr, and after the consent of the patient had been obtained. Plasma was separated and stored deep-frozen until assayed.

Hormone analysis

Testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH) and prolactin were each measured by radioimmunoassay procedures as previously described [6]. A few hormone values were not available for analysis due to the small volume of plasma received. Statistical analysis of the differences between the various survival groups were performed by non-parametric statistics using the Mann-Whitney U test.

RESULTS

Patient grouping

The hormonal data were analysed after grouping the patients according to the number of years they survived from the time of diagnosis of prostatic cancer (Table 1). Further subdivisions were made on the basis of age and also on primary tumour stage and on the clinical evidence of metastases.

Testosterone analysis

The concentrations of testosterone in the plasma of patients, subdivided according to their survival time, are given in Fig. 1. Those patients who died within the first year had significantly lower plasma levels of testosterone than all the other groups of men who succumbed to the disease at later stages ($2P = 2$ yr, 0.009; 3 yr, 0.017; 4 yr, 0.001; and 5 yr, 0.024 respectively) and those patients who were still alive 3–7 yr after diagnosis ($2P = 0.001$). Furthermore, those patients who died within 2 or even 3 yr of diagnosis had pretreatment blood levels of testosterone that were also significantly lower than those men who eventually survived for 3 or more years ($2P = 0.006$ and 0.001 respectively). When data from those patients classified as having T3 primary tumour were analysed (Fig. 2a), individuals who died within the first year of diagnosis had lower mean pretreatment plasma testosterone than those who died 2, 3 or between 4 and 6 yr later ($2P = 0.001$, 0.013, 0.001 respectively) and were also lower than

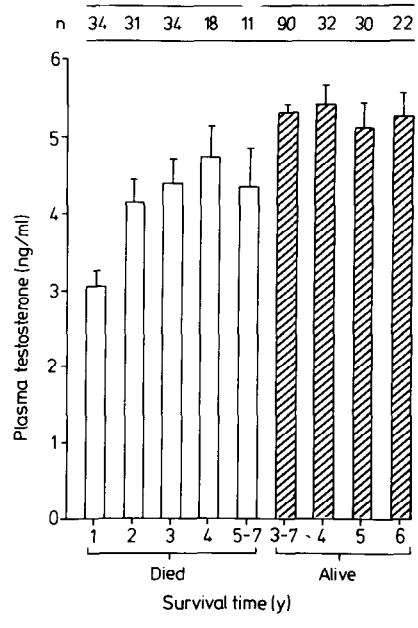

Fig. 1. Pretreatment plasma concentrations of testosterone (mean + S.E.M.) in men with prostatic carcinoma in relation to subsequent length of survival.

Table 1. Patient survival groups (total population)

Survival categories	No. of patients	Mean ages
Patients who died <1 yr after initial diagnosis	34	71.0
,, ,, 1-<2 yr ,, ,, ,,	34	70.3
,, ,, 2-<3 yr ,, ,, ,,	35	70.6
,, ,, 3-<4 yr ,, ,, ,,	18	70.1
,, ,, 3-7 yr ,, ,, ,,	11	68.5
Patients alive 3-7 yr ,, ,, ,,	90	70.7
,, 3-<4 yr ,, ,, ,,	32	70.0
,, 4-<5 yr ,, ,, ,,	30	69.0
,, 5-<6 yr ,, ,, ,,	23	71.3

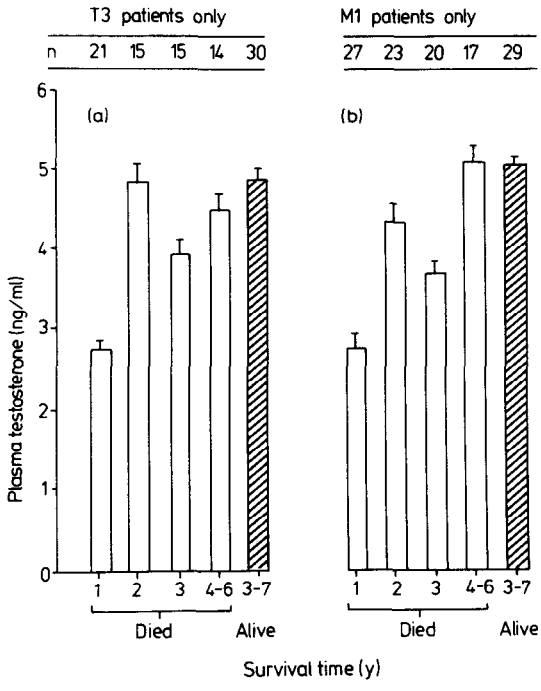

Fig. 2. Pretreatment plasma concentrations of testosterone (mean + S.E.M.) in men with prostatic carcinoma subgrouped as (a) those with a T3 primary tumour and (b) those with clinical evidence of metastases (M1), in relation to length of survival.

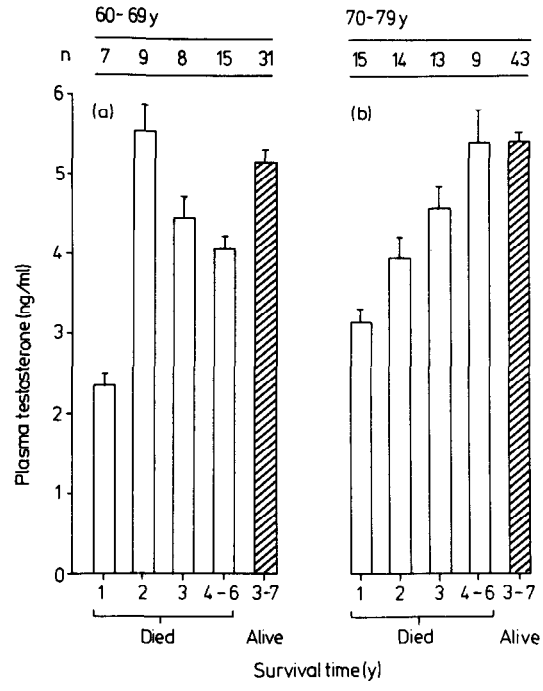

Fig. 3. Pretreatment plasma concentrations of testosterone (mean + S.E.M.) in men with prostatic carcinoma subgrouped according to age (a) 60–69 yr and (b) 70–79 yr, in relation to length of survival from initial diagnosis.

those patients who were still alive between 3 and 7 yr after diagnosis ($2P = 0.0001$). Patients with M1 disease also exhibited this same correlation between pretreatment plasma testosterone concentrations and length of survival (Fig. 2b). Those M1 patients who died within the first year had significantly lower pretreatment testosterone levels than all the other survival groups ($2P = 0.068$ at 2 yr; 0.050 at 3 yr; 0.001 at 4–6 yr; and 0.001 with the group still alive at 3–7 yr).

Patients were also grouped for analysis according to age (60–69 yr and 70–79 yr). Results are shown in Fig. 3. Those patients between 60 and 69 yr of age who died within the first year had lower mean plasma testosterone concentrations than the other groups ($2P < 0.002$, 2 yr; < 0.004, 3 yr; < 0.002, 4–6 yr; and < 0.002 for patients alive 3–7 yr later). After this period, however, no relationship between survival and hormone values was evident (Fig. 3a). In the older patients, however, mean pretreatment plasma testosterone levels were higher as survival time lengthened ($2P < 0.05$ at 4–6 yr; > 0.001 for those patients still alive 3–7 yr) (Fig. 3b).

Luteinizing hormone analysis

Mean pretreatment plasma LH concentrations for the various survival groups are shown in Fig. 4. The prostatic cancer patients who died within 1 yr of initial diagnosis had significantly higher LH concentrations than those who died after 2, 3

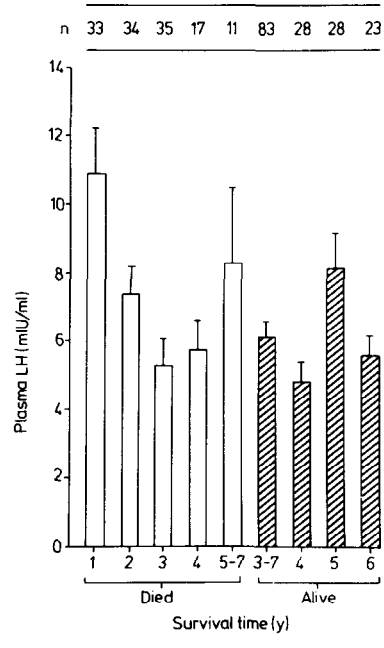

Fig. 4. Pretreatment plasma concentrations of luteinizing hormone (mean + S.E.M.) in men with prostatic carcinoma in relation to length of survival from initial diagnosis.

and 4 yr ($2P = 0.032, 0.001, 0.017$ respectively) and those still alive between 3 and 7 yr after initial diagnosis ($2P = 0.001$). When the patients with T3 category tumours were considered, only those who died within the first year showed a significantly higher pretreatment LH concentration than those patients still alive 5 or more years

later ($2P = 0.136$) (Fig. 5a). Individuals classified as M1 showed no relationship between initial LH concentrations and survival (Fig. 5b). Data from patients subdivided according to age are seen in Fig. 6. In the younger group, 60–69 yr of age, higher LH concentrations were found in those patients who died within 2 yr of diagnosis, although they were not significantly different. Pretreatment LH concentrations in patients aged between 70 and 79 yr bore no relationship to time of survival.

FSH, prolactin and growth hormone analysis

Mean pretreatment plasma FSH concentrations did not correlate with survival, although those patients who died within 1 or 2 yr after initial diagnosis had the highest mean FSH levels. This was observed even when patients were separated into groups according to the staging of the primary tumour, metastatic status or age. No correlation was observed between pretreatment levels of prolactin or growth hormone and the period of survival from initial diagnosis.

DISCUSSION

The results of this study suggest that low plasma testosterone concentrations in men with prostatic carcinoma at the time of initial diagnosis is associated with a poor prognosis. Although the results were based on concentrations of hormone in single plasma samples the variation due to the circadian rhythm of testosterone secretion [11–14] was minimized by sampling as close to 09.00 hr as was possible. The highest levels of plasma testosterone were found in those patients who subsequently survived the longest, a point that was particularly noticeable in the group of 70–79-year-old individuals (Fig. 3b), in those with a T3 primary tumour and in those with metastatic disease. Only those patients in the T3 category and with metastases had adequate numbers in their groups for such an analysis to be performed. It will clearly be interesting to look at the other clinically defined categories, when larger numbers are available.

The observation that high LH concentrations were found at the time of diagnosis in patients who died 1–2 yr later would, together with the low testosterone levels in this group, indicate that the pituitary–testicular axis was no longer functioning normally. One might speculate that those patients with higher levels of plasma testosterone will have prostatic tissue that is maintained at a more differentiated state and will respond to anti-androgen therapy. Similarly, where there is a reduction in functional activity of the pituitary–testicular axis clones of androgen-independent prostatic cells may predominate. The grading of tumours with regard to endocrine status is a study that should be considered following such speculation.

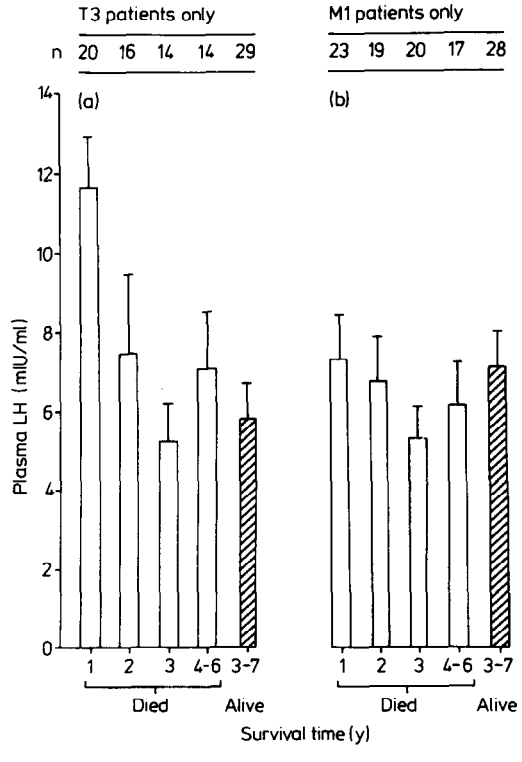

Fig. 5. Pretreatment plasma concentrations of luteinizing hormone (mean + S.E.M.) in men with prostatic carcinoma subgrouped as (a) those with a T3 primary tumour; and (b) those with clinical evidence of metastases (M1), in relation to length of survival.

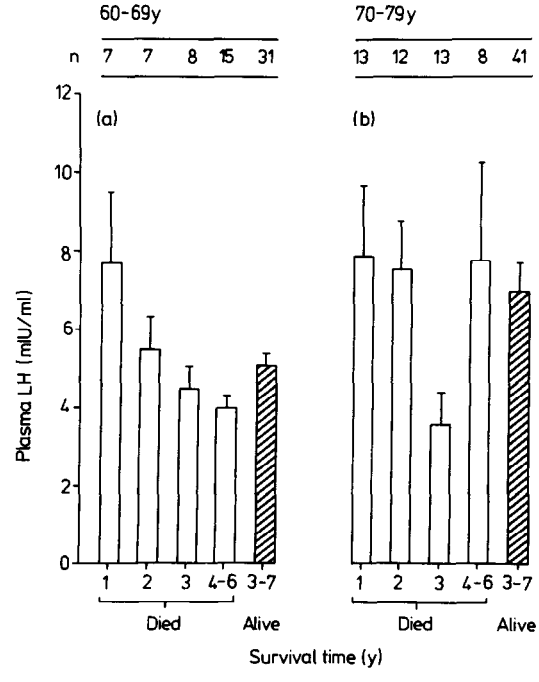

Fig. 6. Pretreatment plasma concentrations of luteinizing hormone (mean + S.E.M.) in men with prostatic carcinoma subgrouped according to age (a) 60–69 yr and (b) 70–79 yr, in relation to length of survival.

It is not surprising that M1 and T3 category patients form the major proportion of individuals who died from prostatic cancer since these clinical parameters are themselves indicators of a poorer prognosis. But it can be seen that even with the T3 and M1 groups of patients, differing survival times were observed that related to the hormone concentrations in plasma. All the patients received endocrine therapy as their primary form of treatment, but in the light of these findings it would obviously be pertinent to study the length of survival of individuals who receive other forms of therapy. A further factor to be considered is the effect of advanced diseases, irrespective of site, on testicular activity. Young and Kent [15] found lower plasma testosterone levels in 10 patients with cancer in sites other than the prostate, and also in 10 patients with non-malignant chronic diseases, than in the patients with advanced prostatic cancer that were studies. Robinson and Thomas [16] found that patients with advanced metastatic disease had lower testosterone concentrations, but although a group with T3M1 disease with a low mean testosterone value was encountered here, another group of 14 patients staged T3M1 had normal to high testosterone values and survived longer. Houghton and Jacobs [17] found no relationship between the 6-month response to orchidectomy and pretreatment LH and testosterone concentrations. Perhaps these contrary findings are due to dissimilar criteria, as in this communication death from prostatic cancer is the end point.

In this investigation, although the concentration of FSH in plasma was higher in patients dying within 2 yr of diagnosis, these did not reach the level of significance. Neither plasma prolactin nor growth hormone concentrations were found to relate to survival, although the studies of Aldercreutz and his colleagues [9] indicated that prolactin concentrations in association with testosterone concentrations related to primary response to endocrine therapy.

The British Prostate Study Group investigation [6] on plasma hormones in relation to clinical stage indicated that growth hormone levels were highest in those patients with M1 disease, but there appears to be no correlation of the plasma concentration of this hormone with survival time from this study.

It is possible that a discriminant function based on hormone concentrations and other clinical features of known prognostic value could be devised which might be beneficial in selecting patients for the most appropriate therapy. The clinician may well consider employing forms of therapy such as irradiation or chemotherapy for the group of patients that present at onset with low levels of plasma testosterone and elevated LH concentrations.

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