Original Article

Review of Clinical Manifestations of Biochemically-advanced Prostate Cancer Cases

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OBJECTIVE: To review the pattern of initial clinical manifestation of patients who present with biochemically-advanced prostate carcinoma.

METHODS: A review of 39 prostate cancer patients with initial prostate specific antigen (PSA) levels of more than 400 ng/mL (study group) and 40 patients whose initial PSA levels were between 20 and 399 ng/mL (control group) was done.

RESULTS: The epidemiological profile and median Gleason score were similar in both groups. In the study and control groups, the median initial PSA levels were 1,000 ng/mL (range, 400–20,000 ng/mL) and 83 ng/mL (range, 21.8–337 ng/mL) respectively. Patients in the study group had statistically significantly higher incidences of bone pain, weight loss, loss of appetite, weakness in the lower limbs, and findings of abnormal prostate on digital rectal examination than patients in the control group. Significantly higher morbidity, including spinal cord compression, systemic lymphadenopathy, chronic urinary retention, elevated serum creatinine levels, anaemia and bone metastases, were also seen in the study group compared to the control group. Similar proportions of patients in the two groups developed hormone escape after treatment (50% in the study group, 45% in the control group). The cancer-specific mortality rate was 39.5% in the study group and 17.5% in the control group.

CONCLUSION: There is a high incidence of excess morbidity in patients who present with biochemically-advanced prostate carcinoma. [*Asian J Surg* 2005;28(3):202–6]

Key Words: prostate neoplasms, prostate specific antigen

Introduction

In Asia, there are still many men with prostate cancer who present with locally advanced and/or metastatic disease at the time of initial diagnosis. The prognosis then becomes dismal in spite of treatment and such men suffer excess morbidity. The mean survival of 3–3.5 years is a pale contrast to the figure of 74–93% 10-year cancer-specific survival for those whose cancer was organ-confined.[1] Serum prostate specific antigen (PSA) levels have been studied extensively; low levels indicate a prognostically more favourable situation due to localized tumour, whereas a high level signals a generalized disease with a short life expectancy.[1] The association between PSA level and tumour spread and symptoms is an important but not yet fully answered question. We propose that patients' initial serum PSA level at presentation can reflect disease load, manifesting as various morbid complications. There is currently no study that reviews the correlation between serum PSA levels and tumour-associated morbidity. In this study, we aim to review the pattern of initial clinical manifestation of patients who present with biochemically-advanced prostate carcinoma and their median survival.

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Patients and methods

A review of the case records in our institution's oncology database of patients with prostate carcinoma between 1988 and 2003 was conducted. Based on these records, patients who had histologically confirmed carcinoma of the prostate and who were diagnosed as having locally advanced or metastatic cancer and a very high initial serum PSA level at the time of first presentation were selected for more detailed review. An arbitrary cut-off serum PSA level of 400 ng/mL or more was used to reflect a hundred-fold increase over the upper limit of 4 ng/mL. Records that had incomplete data or patients who had no histological confirmation were excluded.

A total of 39 cases satisfied the above criteria. Records for another 40 patients with PSA levels between 20 ng/mL and 399 ng/mL were also reviewed for comparison. All analyses were performed using the SPSS statistical package (SPSS Inc, Chicago, IL, USA); data are reported as mean or median, and ranges. Chi-squared and Fisher's exact tests were used for categorical variables, Spearman's correlation was used for quantitative variable determination, and the Mann-Whitney U test was used to determine differences in the means of quantitative variables.

Results

The mean presenting age of the patients with PSA 400 ng/mL or more (study group) was 70 years (range, 52–86 years), and the percentages of ethnic Chinese, Malays, Indians and Caucasians were 76.3%, 15.8%, 2.6% and 5.3%, respectively. For patients with PSA 20–399 ng/mL (control group), the epidemiological profile was similar: the mean presenting age was 72 years (range, 53–87 years) and the percentages of ethnic Chinese, Malays and Caucasians were 82.5%, 15.0% and 2.5%, respectively. None of the patients reviewed had a history of prostate carcinoma in their immediate families. The median initial serum PSA level for the study and control groups were 1,000 ng/mL (range, 400–20,000 ng/mL) and 83 ng/mL (range, 21.8–337 ng/mL) respectively. The median Gleason scores for the study and control groups were 8 (range, 3–10) and 7 (range, 2–10), respectively (Table). Histological diagnosis was obtained using transrectal ultrasound-guided biopsy of the prostate (study group, 52.6%; control group, 65%), histology of prostatic chips obtained from transurethral resection of the prostate (TURP) (study group, 31.6%; control group, 32.5%), bone biopsies of metastases (study group, 5.3%; control group, 2.5%) or core biopsies of systemic lymph nodes (study group, 10.5%). Correlation between PSA levels and Gleason grade scores, using Spearman's correlation, was significant for the control group ($r = 0.348$, $p < 0.05$ [2-tailed]), but the correlation was not significant for the study group.

Common presenting symptoms in both groups, in descending order of frequency, are detailed in Figure 1; 65.8% of patients in the study group and 27.5% of patients in the control group had more than one presenting symptom. Comparisons made using the Chi-squared test revealed that patients in the study group were significantly more likely to present initially with bone pain ($p = 0.004$; odds ratio [OR], 4.9; 95% confidence interval [CI], 1.6–15.1), loss of weight and appetite ($p = 0.014$; OR, 10.1; 95% CI, 1.2–83.3) and weakness in the lower limbs ($p = 0.002$; relative risk [RR], 1.26; 95% CI, 1.07–1.47) compared to those in the control group.

The physical findings at presentation of patients in both groups are shown in Figure 2. Patients in the study group were

Table. Biological features, hormone escape characteristics and mortality data for patients with biochemically-advanced prostate cancer ($n = 79$)

	Control group ($n = 40$) Initial serum PSA, 20–399 ng/mL	Study group ($n = 39$) Initial serum PSA, ≥ 400 ng/mL
Mean presenting age, yr	72 (range, 53–87)	70 (range, 52–86)
Median initial serum PSA, ng/mL	83 (range, 21.8–337)	1,000 (range, 400–20,000)
Median Gleason score	7 (range, 2–10)	8 (range, 3–10)
Hormone escape, %	45	50
Mean time to hormone escape, mo	7.5 (range, 3–60)	12 (range, 2–102)
Overall mortality rate, %	45	50
Mean time to overall mortality, mo	41.9 (range, 12–132)	81 (range, 1–972)
Cancer-specific mortality rate, %	17.5	39.5

PSA = prostate specific antigen.

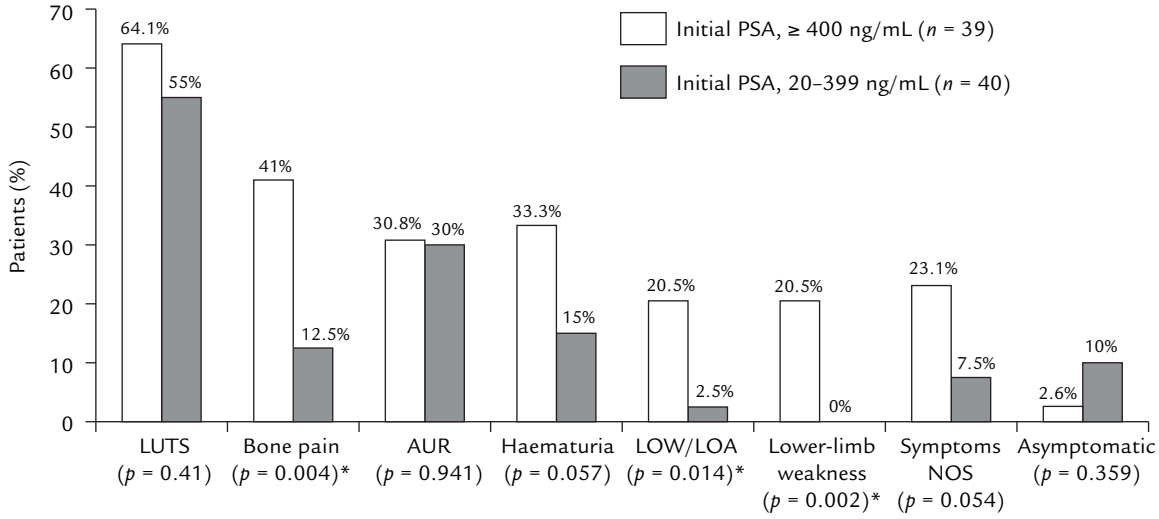

Figure 1. Common presenting symptoms of patients with biochemically-advanced prostate cancer. Comparisons between control and study groups were made with the Chi-squared test (n = 79). *Statistically significant at $p < 0.05$. LUTS = lower urinary tract symptoms; AUR = acute urinary retention; LOW/LOA = loss of weight/loss of appetite; NOS = not otherwise specified.

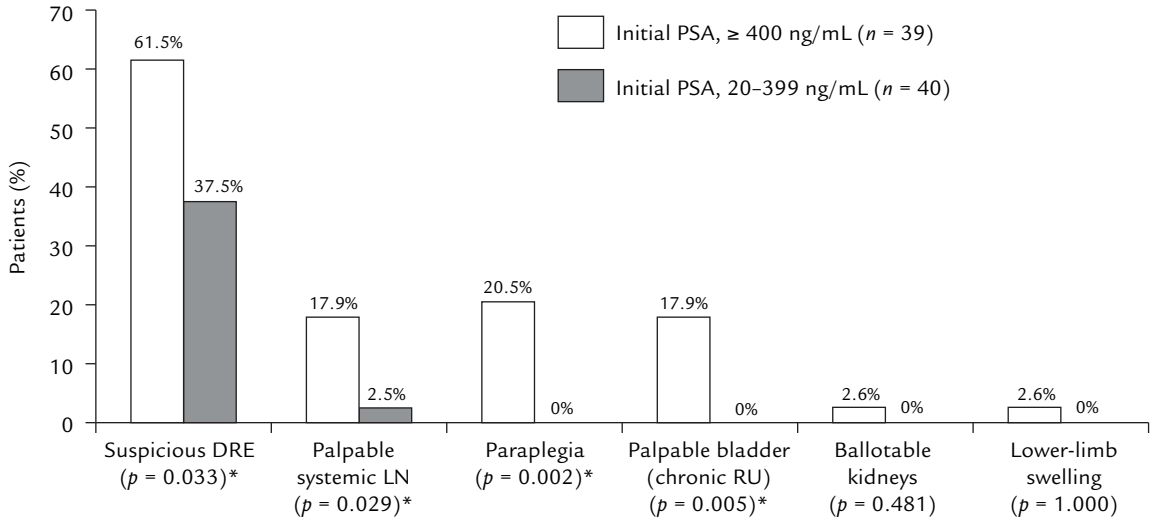

Figure 2. Common initial physical findings in patients with biochemically-advanced prostate cancer (n = 79). Comparisons between control and study groups were made with the Chi-squared test (n = 79). *Statistically significant at $p < 0.05$. DRE = digital rectal examination; LN = lymphadenopathy; RU = retention of urine.

more likely to have suspicious findings from digital rectal examination of the prostate (p = 0.033; OR, 27.0; 95% CI, 1.1–6.6), palpable systemic lymphadenopathy (p = 0.029; OR, 8.5; 95% CI, 1.01–71.4), paraplegia (p = 0.002; RR, 1.26; 95% CI, 1.07–1.47) and a palpable bladder, reflecting chronic urinary retention (p = 0.005; 95% CI, 1.05–1.41) compared to those in the control group. All patients in the study group and only one patient in the control group who had clinically palpable generalized lymphadenopathy (axillary, cervical or inguinal nodes) also had enlarged intra-abdominal or intrathoracic lymph nodes seen on computed tomography (CT) or magnetic resonance imaging (MRI). Eight patients in the study group presented with paraplegia, whereas none did in the control group, but this was not statistically significant.

At presentation, 10 (25.6%) patients in the study group and three (7.5%) in the control group had elevated serum creatinine levels; this difference was statistically significant (p = 0.03; OR, 4.3; 95% CI, 1.1–16.9). Of the patients in the study group who had elevated serum creatinine levels, only 50% were related to renal hydronephrosis, while 66.7% of those who had renal hydronephrosis had elevated serum creatinine levels. Patients in the study group were significantly more likely to present with anaemia (haemoglobin level < 11 g/dL) compared to those in the control group (p = 0.008; OR, 5.5; 95% CI, 1.4–

21.3). Bone metastases diagnosed via bone scans were also more common in the study group compared to the control group ($p < 0.001$). Eight patients in the study group who had back pain and weakness in the lower limbs were found to have spinal cord compression on MRI, while there was no incidence of cord compression in the control group; this difference was significant ($p = 0.002$; RR, 1.26; 95% CI, 1.07–1.47). The difference between the two groups in significant coagulopathy, reflected by abnormal clotting profile and/or decreased serum platelet counts, bacteriuria, hydronephrosis and incidence of enlarged intra-abdominal or intrathoracic lymph nodes on CT or MRI scans were not significantly different (Figure 3). All patients in the study group who had clinically palpable generalized lymphadenopathy (axillary, cervical or inguinal nodes) also had enlarged intra-abdominal or intrathoracic lymph nodes seen on CT or MRI scans. This was the case for only one patient in the control group.

Anti-androgen medical therapy was the initial treatment for 47.4% of study group patients and 47.5% of control group patients; the remaining patients were treated with surgical castration. Palliative radiotherapy to bone metastases was administered to 47.4% and 5% of study and control group patients, respectively. Prostate radiotherapy was administered to 12.5% of control group patients. In the study group, two patients had bilateral percutaneous nephrostomy drainage and antegrade double-J ureteric stents inserted to relieve upper tract obstruction. Fifty percent of patients in the study group and 45% of patients in the control group developed hormone escape ($p = 0.58$). Mean time to hormone escape for study and control group patients were 12 months (range, 2–102 months) and 7.5 months (range, 3–60 months) after initial hormone treatment, respectively ($p = 0.191$). The mortality rate in the study group was 57.9% after a mean of 81 months (range, 1–972 months), while the cancer-specific mortality rate was 39.5%. The mortality rate in the control group was 20% after a mean of 41.9 months (range, 12–132 months), while the cancer-specific mortality rate was 17.5% (Table). There were no statistical differences in survival parameters between the two groups (Mann-Whitney U test, $p = 0.26$).

Discussion

In patients with advanced prostate cancer, data in the literature indicate a mean survival of 3–3.5 years, and patients with minimal metastatic load having an expected survival of 4–6 years.[1] Endocrine treatment is still currently regarded as palliative, and it is controversial as to whether endocrine therapy can prolong survival.[1] Serum PSA has been shown to be a sensitive and, currently, the most useful marker for prostate cancer in terms of detection, staging and monitoring response to therapy.[1–6] Serum PSA levels have also been shown to correlate directly with advancing clinical and pathological stage of prostate cancer,[3,7–10] although PSA level alone may not provide for accurate staging due to the overlap in PSA

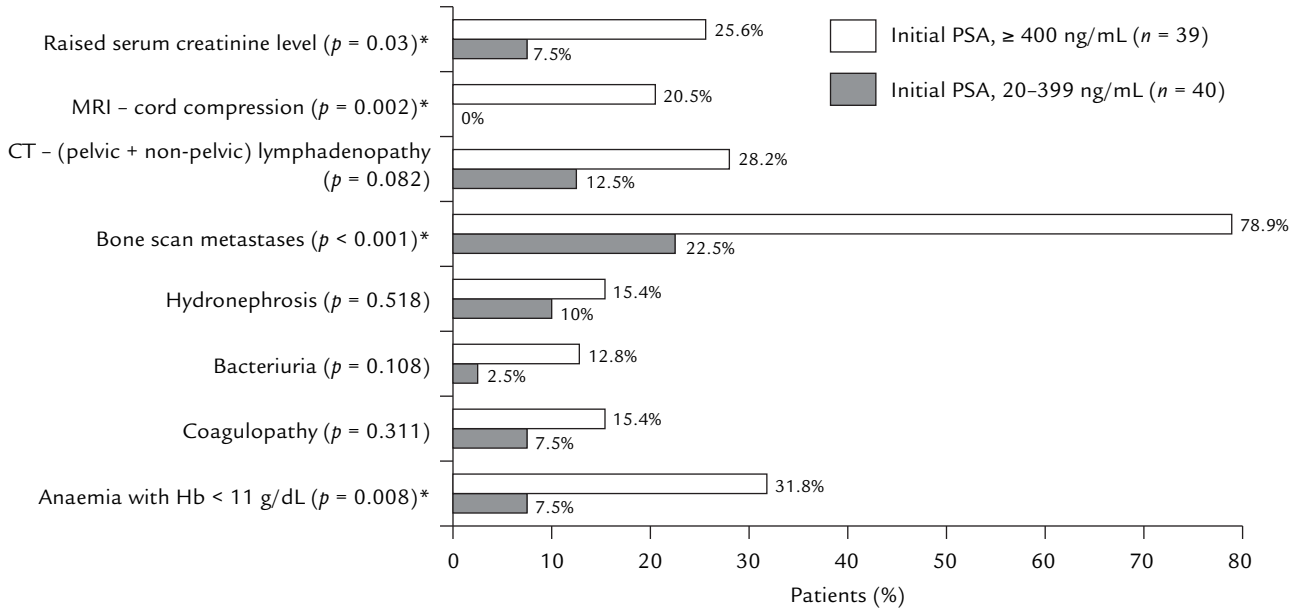

Figure 3. Investigative laboratory and imaging findings in patients with biochemically-advanced prostate cancer ($n = 79$). Comparisons between control and study groups were made with the Chi-squared test ($n = 79$). *Statistically significant at $p < 0.05$. MRI = magnetic resonance imaging; CT = computed tomography; Hb = haemoglobin.

levels between stages.[2] It has been shown that a serum PSA level of less than 10 ng/mL indicates a higher likelihood of organ-confined cancer, and more than 50% of men with PSA levels above 10 ng/mL have extraprostatic disease.[10,11] This report aimed to outline the incidences of the various morbidities of advanced prostate carcinoma so that clinicians can be more aware of the common complications and problems in patients with biochemically-advanced prostate carcinoma.

In our group of prostate cancer patients presenting initially with very high serum PSA levels (> 400 ng/mL), we found that more than half had multiple symptoms at presentation, while this was so in only one-quarter of the control group patients (PSA between 20 and 399 ng/mL). Local prostatic symptoms of lower urinary tract symptoms, acute urinary retention and haematuria were common in both study and control group patients. In the study group, bone pain, weakness in the lower limbs, weight loss, and loss of appetite were present at significantly higher rates than in the control group, reflecting the manifestation of disease burden not just at the prostate but also at the systemic level. Comparing physical findings and investigation results at initial presentation for both groups of patients also revealed a similar observation of study group patients having more systemic manifestations than control group patients. An interesting observation was that about one-third of our study group patients had clinically palpable systemic lymphadenopathy, and this correlated with a high incidence of intracavity (intra-abdominal or pelvic) lymph node enlargement as well. This observation was, however, not so well seen in the control group. The incidences of renal impairment and anaemia were significantly higher in the study group than in the control group, while bilateral hydronephrosis, coagulation abnormalities and systemic lymphadenopathy were also present in a fairly high percentage of study group patients. In patients with very high initial serum PSA levels (study group), we also observed that bone metastases occurred in 78.9% of patients, and the incidence of spinal cord compression was 20.5%. Patients with lower initial serum PSA levels (control group) had a significantly much lower percentage of bone metastases, with none of them having cord compression.

Aside from hormone treatment, radiotherapy to bone metastases and channel TURP were the most common palliative therapies instituted for both groups of patients. The indications for TURP were mainly to help wean patients off urinary catheters for significant urine retention, to alleviate symptoms of haematuria, and to relieve upper tract obstruction. Percutaneous nephrostomies for hydronephroses or spinal cord decompression were not performed for all affected patients as these patients were deemed to be terminally ill with a poor prognosis. The prostate cancer-specific mortality rate was 39.5% in the study group, which was similar to reported literature;[12] it was lower at 17.5% in the control group.

In conclusion, this report highlighted a high incidence of morbidity, especially systemic manifestations of cancer, in patients with biochemically-advanced prostate carcinoma who present with very high initial serum PSA levels of 400 ng/mL or more, compared to those with lower initial serum PSA levels. The various incidence figures should prove to be useful in increasing awareness of the excess morbidity that these patients might suffer from.

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