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Evaluation of prostate specific antigen in the prognosis of patients with advanced prostate cancer

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Objective: To evaluate the survival rate of patients with advanced prostate cancer in a univariate form, according to the preoperative and first postoperative determination of PSA levels. **Materials and Methods:** From February 1987 to June 1995, 92 patients were submitted to maximum blockage androgen (subcapsular and antiandrogen orchiectomy), independent of clinical symptoms shown upon admission to the Cancer Hospital. The antiandrogens (ciproterone acetate and flutamide) were administered until the patient present progression of the disease. **Results:** The age of patients varied from 44 to 89, with a median of 70 years old. In the 6th, 36th and 60th months the global survival rate was 80%, 38% and 20%, respectively. The preoperative PSA ranged from 2 to 4017 ng/ml, with a median of 98 ng/ml (98% had PSA greater than or equal to 10 ng/ml). The first postoperative PSA ranged from 1 to 3840 ng/ml, with a median of 20 ng/ml. There was a tendency towards a better survival rate only in patients with initial PSA from 2 to 99 ng/ml ($p=0.06745$). The survival rate of patients at 36 months after the initial total blockage androgen, with first PSA level from 1 to 4, 5 to 49 and over 49 ng/ml was 72%, 48% and 8%, respectively ($p=0.00004$). In the final examination, 34 (37%) patients were considered stable and 58 (63%) had disease progression. **Conclusion:** The PSA determination performed on the 30th postoperative day is important in the evaluation of advanced prostate cancer prognosis.

Uniterms: PSA. Advanced prostate cancer. Maximum blockage androgen. Prognostic factors.

INTRODUCTION

The prostate specific antigen (PSA) is a glycoprotein with molecular weight of approximately 31,000 Daltons. It was isolated in prostate tissue and identified in seminal plasma by Wang et al. in 1979. It is produced by epithelial cells of the ducts and acinus of the normal prostate in the event of hyperplasia or cancer, being involved in the liquefaction of the seminal coagulum.¹ PSA is useful in staging and monitoring of therapeutic responses and in evaluating the

prognosis of the disease. Ercole et al. showed that 98% of patients with stage D2 have a high PSA level.² There is a direct correlation between the volume of the cancer and PSA level, with high PSA values being indicative of clinically advanced cancer.³⁻⁵

The sensitivity of PSA in the evaluation of disease progression in patients with advanced cancer is $86.7 \pm 3.1\%$, with a specificity of $92.4 \pm 4.1\%$. Its accuracy is $89.2 \pm 1.7\%$.⁴ PSA is significantly better than prostatic acid phosphatase for the detection of recurrence in patients under hormonal therapy. An increase in PSA can occur up to 12 months before detection by other methods.^{4,6}

The prognosis of patients with advanced prostate cancer has been evaluated by clinical-pathological and biochemical parameters with variable results. These parameters have included: age, Karnofsky index, volume and extent of local and distant disease (number of bone metastases), histological grade (by Mostofi classification and/or Gleason score), nuclear ploidia,

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preoperative testosterone blood level, dosage of androgenic receptor in the tumor, change of prostatic volume via transrectal ultrasound after androgen suppression, and dosage of prostatic acid phosphatase, amongst others.^{2,3,4,5,7}

In the present study we retrospectively analyzed the survival rate of patients with advanced prostate cancer in a univariate form, according to the preoperative and first postoperative PSA levels.

METHODS

From February 1987 to June 1995, 92 patients with advanced prostate cancer were admitted because of positive histopathology and bone scintillography (M1 staging of TNM classification, 1987).⁸ All patients were submitted to maximum blockage of androgen (orchiectomy and antiandrogen treatment with ciproterone or flutamide, at a dosage of 150 and 750 mg/day, respectively). The subcapsular orchiectomy was performed on all patients, independent of the clinical symptoms presented at admission.

Initial evaluation was made via history, physical examination, prostate and abdomen transrectal ultrasounds, bone scintillography and chest X-Ray, dosage of PSA, alkaline phosphatase, total and prostatic acid phosphatase. Urography and computerized tomography were performed only when indicated.

The follow-up was monthly and all general complaints and urinary symptoms were evaluated. At this time the antiandrogen drugs to be used during the following month were given to the patient. The subsidiary tests were requested according to clinical indications, but PSA was evaluated on the 30th postoperative day and every three months thereafter. The PSA evaluation was performed at the same laboratory and with the same immunoassay (Hybrytech Tandem-R). Of the 92 patients included in the study, it was possible to evaluate PSA for the preoperative and first postoperative periods in 68 and 80 patients, respectively.

Response criteria: The therapeutic response was evaluated according to the criteria of the National Prostatic Cancer Project⁹ and the level of PSA after the beginning of the treatment. Stabilization or progression of the disease was considered according to the sequential level of PSA and prostatic phosphatase, bone scintillography and overall clinical conditions. The patient was considered stabilized if the last PSA was lower than the previous one.

Progression of the disease was determined by the disease symptoms, biochemical assays, bone scintillography

and whether the last PSA was better than the previous one. Disease progression was considered to have occurred if one or more of the following symptoms were present: onset or worsening of bone pain, increase of prostatism, rachimedullary compression, use of inflammatory, analgesic and narcotic drugs, palliative radiotherapy, detection of new visceral and/or bone metastases, coagulopathy, bone medullary suppression, ureteral obstruction etc.

Statistical analysis. For all actuarial analyses of the overall survival rate, the KMSURV computer program was used.¹⁰ In this program, the estimated actuarial survival rate is obtained using the Kaplan & Meier limiting product technique. Comparisons between survival rates for different categories of variables were performed using the Cox-Mantel tests.¹⁰ The overall survival time was considered in months, from the date of surgery until death or until the last date of follow-up.¹¹

The final evaluation of the patients was made by analysis of reports from June 1995. The overall survival curve was plotted using the dates when patients had been submitted to orchiectomy, with the PSA dosage at preoperative and first postoperative times. We arbitrarily divided preoperative and postoperative PSA levels into three stages to construct the curves and analyze the statistical significances amongst them. The curve was drawn by computer program.

RESULTS

The age of patients ranged from 44 to 89 with a median of 70 years old. The distribution of patients by age range was: 44 to 60, 61 to 70 and over 71 years old, with 15, 29 and 48 patients, respectively. In the 6th, 36th and 60th month the overall survival rate was 80%, 38% and 20%, respectively (Fig.1). Seventy-nine patients (85.9%) showed less than 20 bone metastases, eight patients (8.7%) more than 20 metastases and in five patients (5.4%) no count was possible.

Preoperative PSA was evaluated in 68 patients (73.9%). In these cases PSA ranged from 2 to 4017 ng/ml, with a median of 98 ng/ml. Ninety-seven percent of the patients had a PSA higher than or equal to 10 ng/ml. The distribution of patients by PSA level, from 2 to 99, 100 to 499 and over 499 ng/ml was respectively 35, 15 and 18 patients ($p=0.06745$) (Fig. 2).

The first postoperative PSA data was collected from 30 to 45 days after the orchiectomy and was performed in 80 patients (86.9%). In these patients, the first postoperative PSA ranged from 1 to 3840 ng/ml, with a

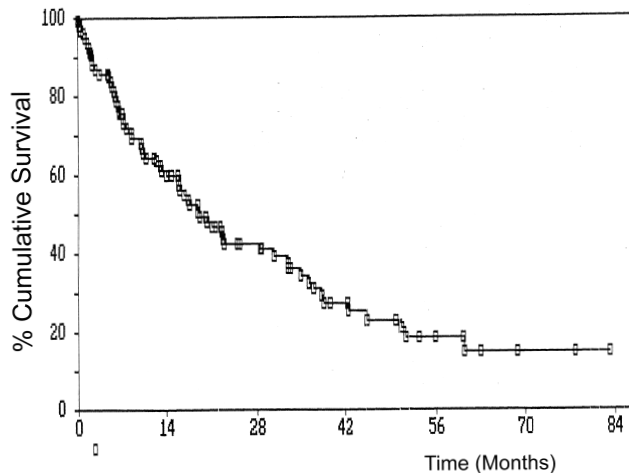


Figure 1 - Overall survival rate of patients submitted to maximum androgen blockage (92 patients).

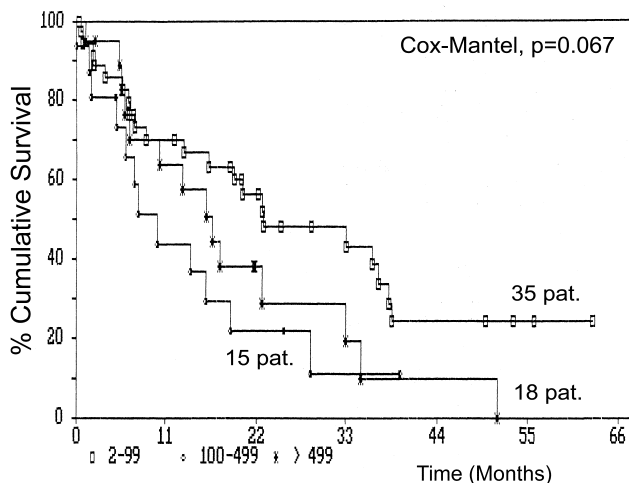


Figure 2 - Survival according to pre-operative PSA (68 patients).

median of 20 ng/ml. The distribution of patients by first post-orchietomy PSA level divisions of 1 to 4, 5 to 49, and over 49 ng/ml was 27, 22 and 31 patients, respectively ($P=0.00004$). During the last examination 34 (37%) patients were considered stable and 58 (63%) having progression of the disease. Among the 35 surviving patients, 9 (9.8%) were asymptomatic and 5 (5.6%) with active cancer. Sixty-two (67.4%) of the patients died and 16 (17.4%) did not return to the hospital.

DISCUSSION

Androgen is essential for prostate trophism. In its absence the gland does not grow, does not differentiate or

maintain its size or function. Bilateral orchiectomy is the gold standard treatment for advanced prostate cancer.¹¹ Three hours after surgery, the testosterone levels drop to 90-95% of the initial value, with levels ranging from 10 to 50 ng/ml.^{12,13} The drop in testosterone causes the death of well-differentiated neoplastic cells (patients with low Gleason score and/or diploid neoplastic cells). Therapeutic response is observed in 80-85% of the patients, but 15-20% may continue to be resistant after the onset of therapy. The survival rate of the treated patients in the 6th, 36th and 60th month is 90%, 50% and 30%, respectively.³

Maximum androgen blockage in the treatment of advanced prostate cancer may produce a small but significant increase in disease-free time and survival (an average of 6 months), thus temporarily improving the quality of life. The benefit may be greater in patients with minimal disease and better clinical performance. Hormonal therapy has been found to be a palliative approach rather than a cure.^{12,13} The survival rate for patients in the current study treated with maximum androgen blockage in the 6th, 36th and 60th months is 80%, 38% and 20%, respectively. The 20% mortality rate in our study, six months after maximum androgen blockage, suggests a worse clinical status for the patients and a higher rate of metastatic disease at the initial moment of the treatment.

PSA is greater than 4 ng/ml in 88% of the patients at stage D2.¹⁴ In this retrospective study, 97% of the patients (66 out of 68) had PSA greater than 4 ng/ml. Sixty patients (88.2%) had PSA greater than 20 ng/ml. This confirms the findings by other authors that PSA alone is not sufficient to determine the clinical stage. PSA over 100 ng/ml suggests a locally advanced cancer or a metastatic disease.^{2,5,7,15}

Patients with low blood concentration of PSA (20 ng/ml) seldom have bone metastases. The negative predictive value is 99.7% and suggests that bone scintillography may not be necessary for the initial evaluation in new cases.¹⁶ In the present study, 8 out of 68 (11.7%) patients had PSA lower than 19 ng/ml in the preoperative period.

The initial PSA level (preoperative) is inverse to the survival rate of patients with D2 stage cancer.^{5,6} In the present study there was a tendency towards longer survival rates only in patients with PSA from 2 to 99 ng/ml ($p=0.06745$). The level of PSA after surgery appears to be the best way to evaluate the survival rate.^{6,14} There is a tendency towards low PSA until sixth months after treatment.^{14,17,20} Patients with a suitable response (longer survival rate) after hormone therapy usually have PSA under 4 ng/ml in the first three months after the initial treatment.⁶ When there is a PSA concentration less than 4 ng/ml, three months after treatment, the average time to

disease progression is 30 months and the survival rate is over 36 months. With PSA greater than 4 ng/ml, the average time to disease progression is 17.5 months and the survival rate is 28.5 months.¹⁸ In this study, the survival rate of patients during the 36 months after the initial maximum androgen blockage, subdivided into PSA levels from 1 to 4, 5 to 49 and over 49 ng/ml was 72%, 48% and 8%, respectively ($p=0.00004$).

Patients with metastatic disease of the prostate are heterogeneous in relation to the initial disease (differences in histological grades, nuclear ploidy, number of bone metastases, initial testosterone levels, age, etc).^{3,5,19} PSA can contribute to the separation of patients into subgroups at the same stages and, together with other clinical, laboratorial and radiographic parameters, to the determination of the prognosis and therapeutic response.

The production of PSA is regulated by hormonal mechanisms and controlled by androgen action in the cellular receptors. LNCaP cells in culture with dihydrotestosterone produce a significant increase in PSA, by mRNA production and glycoprotein-PSA biosynthesis. This production can be reduced in the presence of antiandrogen (androgen blockage receptors).¹⁷ With

increasing Gleason score (undifferentiated cancer), the PSA level per unit of tumoral volume decreases.¹⁸

The reduction in PSA after hormonal treatment depends on the decrease in its production, fundamentally caused by the death of differentiated neoplastic cells of the tumor. An increase in PSA during hormonal treatment (therapeutic escape) begins 6 to 12 months before clinical and radiographical findings demonstrate the progression of the disease. During this period, in accordance with the functional organic reserve of the patients, an alternative therapy may be indicated to reduce progression of the cancer (second-line therapy or experimental new protocols).

In the absence of male hormones the number of independent testosterone cells can increase, leading to progression of the disease without increasing PSA levels (insensitive cells may be unable to express PSA).^{5,16-18,20,21} Then, the evaluation of the therapeutic response of patients with advanced prostate cancer may be made clinically, checking PSA and phosphatase levels every three months, further complemented by bone scintillography, radiography and computerized tomography, whenever indicated.

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RESUMO

De fevereiro de 1987 a junho de 1995, 92 pacientes com câncer de próstata avançado foram submetidos a bloqueio androgênico máximo (subcapsular orquiectomia e antiandrógeno), independente dos sintomas clínicos apresentados na sua admissão. A idade dos pacientes variou de 44 a 89 anos, com mediana de 70 anos de idade. No 6º, 36º e 60º meses, a sobrevida global foi de 80%, 38% e 20%, respectivamente. O PSA pré-operatório variou de 2 a 4017 ng/ml, com mediana de 98 ng/ml e 98% dos pacientes tinham PSA maior ou igual a 10 ng/ml. O primeiro PSA pós-operatório variou de 1 a 3840 ng/ml, com mediana de 20 ng/ml. Neste estudo retrospectivo, 97% e 88,2% dos pacientes tinham PSA pré-operatório maior que 4 e 20 ng/ml, respectivamente. Houve somente uma tendência de melhor sobrevida nos pacientes com PSA inicial de 2 a 99 ng/ml ($p=0,06745$) que com PSA maior que 100 ng/ml. Há uma tendência de diminuição do PSA até o sexto mês depois do início do tratamento. A sobrevida dos pacientes em 36 meses após o bloqueio androgênico máximo, de acordo com o primeiro nível do PSA de 1 a 4, 5 a 49 e maior que 49 ng/ml foi de 72%, 48% e 8%, respectivamente ($p=0.00004$). No último exame, 34 (37%) dos pacientes foram considerados estabilizados e 58 (63%) com progressão da doença.