Four prognostic indices in advanced prostate cancer patients, under palliative androgen deprivation treatment

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Keywords: Gleason score – Prostate specific antigen – Bone scintigraphy – Prostate cancer

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Received:
22 January 2008
Accepted revised:
20 March 2008

Abstract

Prostate cancer (PCa) is the second leading cause of death in men aged 40 years and older and prognostic indices are useful in suggesting its proper treatment. *The aim* of this study was to evaluate the prognostic value of Gleason score (GS), TNM staging system, initial serum prostate specific antigen (PSA) and bone scintigraphy (BS) in patients with PCa under hormonal palliative treatment, in the development and progression of recurrent PCa. *Our methods were as follows*: Between January 2005 and December 2007, we have studied at the University General Hospital of Alexandroupolis fourty patients of mean age 77±7.2 years with advanced PCa under palliative treatment with antiandrogens and luteinizing hormone-releasing hormone analogues. PCa was diagnosed histologically, based on the TNM system after transrectal ultrasonography guided biopsy. The Gleason score assessment was made as described by others. Metastases were confirmed by a positive bone scintigraphy with 925 MBq ^{99m}Tc-MDP using a tomographic gamma camera, computerized axial tomography or magnetic resonance imagining. Measurements of PSA were conducted by the radioimmunoassay method. We also examined 20 healthy blood donors (median age 45±6.1 years) as controls, in order to estimate the cut-off value of PSA. *Our results* show the following: Thirteen of our patients had 1-6 "hot" spots and 27 had more than 6 "hot" spots in the bone scan. The median Gleason score was 7 (modal Gleason score 3+4). Serum PSA levels were higher in patients with PCa and bone metastases in comparison to those with PCa without bone metastases. Very high values of PSA (more than 50 ng/ml) were found in patients with multiple bone metastases (>6 "hot" spots). *In conclusion*, our findings demonstrate that the prognostic value of GS (P=0.043), TNM staging (P=0.1410), serum PSA levels (P=0.002) and BS (P=0.0135) when used alone, not always improve the prognosis to hormone independent but when combined (P<0.001) increase the prognosis in patients with advanced PCa under hormonal palliative treatment.

Hell J Nucl Med 2008; 11(1): 21-25

Introduction

Prostate cancer (PCa) is the second after lung cancer, commonest leading cause of death in men aged 40 years old and older [1]. It is estimated that only in the USA 1 in every 6 men develops PCa during his life, while 1 out of 32 will die of the disease [2].

Despite early detection of the disease, it is estimated that approximately 30% of treated patients will suffer tumour recurrences. Since PCa is hormone dependent, a large group of patients with PCa after prostatectomy undergo palliative androgen deprivation treatment. There are patients with locally advanced, metastatic PCa [3-8] or patients with increased prostatic specific antigen (PSA) [9]. The diagnostic stage and the follow-up of these patients is very important and includes serial bone scintigraphy (BS) and PSA. It has been suggested that PSA estimations may reduce the number of BS [10].

Also the tumour, node and metastases system (TNM), as modified in 1992, is a commonly used, clinical staging index for PCa patients after prostatectomy who undergo palliative androgen treatment [11]. Clinical staging, although not uniformly reproducible, provides a means to distinguish localised from locally advanced and metastatic PCa and is also useful for prognosis because factors indicating poor prognosis such as: tumor volume, surgical margin status, extend of extracapsular spread, involvement of seminal vesicles and pelvic lymph nodes, can be determined [12].

In the above group of PCa patients who undergo androgen deprivation treatment, the diagnosis of the grade of the primary tumor and the likelihood of distant metastases are indicated by the Gleason score (GS) [13]. Low grade PCa may either remain long as such, or after some years, develop high grade tumors [14]. Some believe that PCa starts as a low grade tumor and differentiates to a high grade stage [15]. When the stage of the disease is factored

in with the grade of tumor malignancy, prognosis is enhanced. It has been reported that the GS grade of the tumor after radical prostatectomy or preoperatively also correlates with the final pathologic stage of PCa [16]. Also GS is often used to estimate prostate tissue after trans rectal biopsy [13].

Hormonal treatment of PCa induces shrinkage of cancer tissue which can be shown by the decrease and disappearance of metastatic tissue. Even normal prostate tissue is able to regrow after androgenic stimulation. The possibility of relapse of the primary tumour, as well as for metastases, under hormone treatment may be explained by the presence of hormone independent (HI) cell population and clonal overgrowth of PCa and of normal prostate cells the mechanism of which is poorly understood, eventually leading to the presence of a hormone insensitive tumour [16, 17].

In patients with advanced PCa under androgen deprivation treatment a key factor for staging and prognosis is bone metastases. Some bone metastases can be diagnosed by plain radiographs and/or BS. Plain radiographs are highly accurate when detecting metastatic lesions especially when are painful, however their sensitivity is limited. BS is approximately 50% to 80% more sensitive than plain radiographs. It can frequently show metastatic lesions long before i.e. 2-6 months before plain films findings appear [18-20]. Since in patients with PCa under hormone treatment, prognosis varies, the combination of prognostic factors for HI mentioned above: the TNM staging, biopsy GS, initial PSA and BS that we have studied, considerably increases prognostic efficiency.

Patients and methods

Between January 2005 and December 2007, we have studied at the University General Hospital of Alexandroupolis 40 patients of mean age 77±7.2 years with advanced operated PCa under palliative treatment with antiandrogens and luteinizing hormone-releasing hormone (LHRH) analogues. The time to HI was measured from the time of diagnosis. The follow-up data included: clinical status every three months, occurrence of skeletal events (BS every year), PSA measurements every three months, time to HI, and till death of the patient. The patients were followed up for two years and their latest status was examined. PCa was confirmed histologically based on the TNM system after transrectal ultrasonography (TRUS) guided biopsy [12]. GS assessment was made as described before [13].

For the evaluation of PCa we used the GS grading system witch is based on the glandular histological pattern of the tumor as identified at relatively low magnification. Cytologic features play no role in grading the tumor. Both primary (predominant) and secondary (second most prevalent) architectural patterns, well identified and assigned to a grade 1 to 5, with 1 being the most differentiated and 5 the least differentiated pattern.

Bone metastases were shown by BS and also by CT or MRI imaging. All patients underwent whole body BS with 925 MBq of technetium-99m methyl diphosphonate (^{99m}Tc-MDP) using a tomographic gamma-camera (GE, Millennium MPR, U.S.A). Whole body BS with ^{99m}Tc-MDP is expected to show areas of bone formation after bone metastases and to follow the response to palliative treatment.

PSA was measured by the radioimmunoassay technique (RIA). Blood samples were drawn in the morning after an overnight fast and serum was separated and frozen at -70 °C until assayed. Serum PSA levels were determined by the kit Tandem-R PSA assay (Hybritech Inc. USA). We also examined 20 healthy blood donors (median age 45±6.1 years) as control group, in order to estimate the cut-off value of PSA. Serum PSA measurements during the two years of the follow-up program, were performed every three months and a BS every year. Testing and clinical examinations during the follow-up period was similar to that of other studies [18-20]. All patients' records were reviewed retrospectively. The time of HI and the survival time, were calculated at the time of diagnosis.

Statistical analysis

Analyses were performed using the statistical package SPSS Version 11.00. Statistical analyses of the TNM stage, GS, serum PSA values and BS were performed using the chi-squared test and the time to disease progression to HI, were calculated by using the Kaplan-Meier method. A *P* value of less than 0.05 was considered to be statistically significant.

Results

Patients' characteristics presented are summarized in Table 1. PCa tumors in 23 (57%) of our patients' were encapsulated in one prostate lobe (T2) or in both (T3). Seventeen patients (43%) presented with unilateral (T3a) or bilateral extraprostatic (T3b) extension of the cancer or invasion by the tumor of another organ such as the seminal vesicles (T3c), the bladder neck, the rectum, the external sphincter (T4a) the levator muscle, or the pelvic floor (T4b). Seven of the above 7/17 or 18%

Table 1. *Patients' characteristics.*

Age (M)	58-96	77±7,2
TNM	No	%
T1-T2	23	57
T3-T4	17	43
N0/N1	33/7	82/18
M0/M1	35/5	87/13
Gleason score		
≥ 7	13	32
< 7	27	68
Bone scan (Hot spots)		
$T_{1-4}N_{0-1}M_{0-Mb}$		
≥ 6	12	30
≥ 6	12	30
Initial PSA levels (ng/ml)		
≤ 50	22	55
> 50	18	45
Total	**40**	**100**

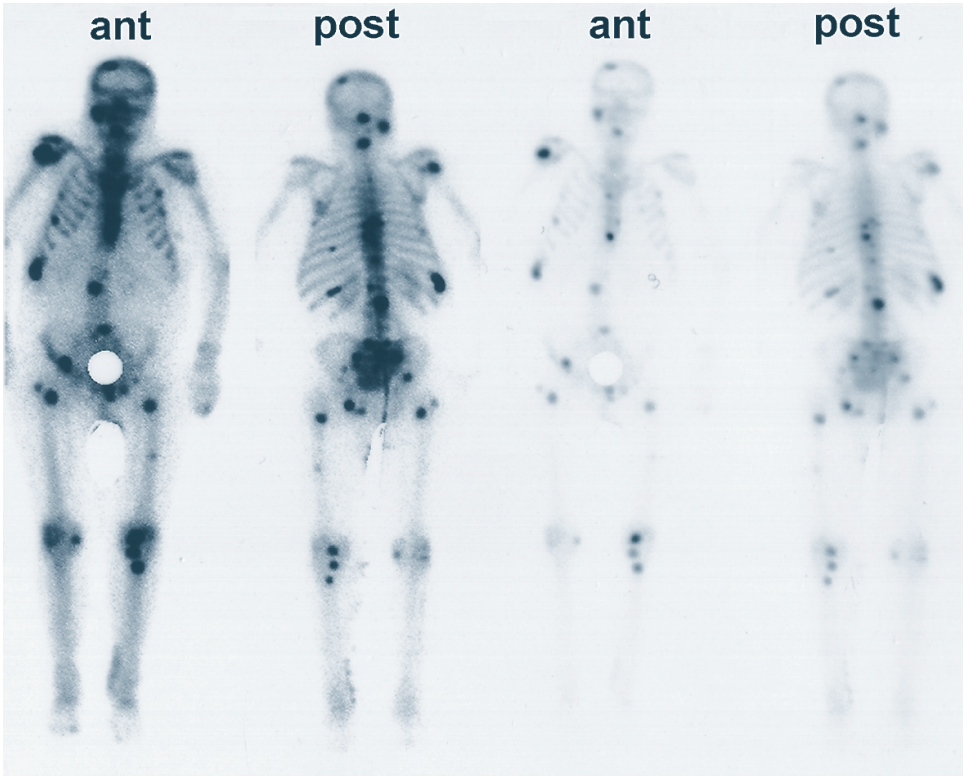

Figure 1. Whole body bone scan with 925 MBq ^{99m}Tc-MDP in a patient with skeletal metastases of prostate cancer with more than 6 hot spots on a bone scan.

of our patients had nodal metastases and 5/17, 13% had visceral metastases. Thirteen of all patients presented with ≥ 6 hot spots and 27 with < 6 hot spots after a bone scan (Fig. 1). The median GS was 7 (modal GS 3+4). A significant proportion of our patients, 27 (68%) presented with low GS (<7) and 13 (32%) with high GS (≥7).

The range of the initial serum PSA value was 3.2 to 450.0 ng/ml (mean 56.5 ng/ml). Serum PSA levels were higher in patients with bone metastases (T_{1-3} N_{1-3} M_{1b}) in comparison to patients without bone metastases. Very high values of PSA (more than 50 ng/ml) were found in patients with multiple bone metastases (more than 6 hot spots).

A multivariate analysis of factors increasing the risk for progression of PCa to HI including initial serum PSA levels, stage, GS, and the hot spots localised by multiple bone scans is shown in Table 2. Fourteen patients (35%) developed HI during a period of 24 months of follow-up after the diagnosis of metastatic PCa (Table 2). Ten (71%) patients with TNM stage T_3-T_4 N_0-$_1M_{0-1b}$ developed HI in 15 months and ten patients with GS ≥ 7 developed HI in 12 months (Table 2). Four patients (29%) with initial serum PSA value when higher than 50 ng/ml (P=0.002) (Fig. 2) and six (42%) patients with BS with more than six hot spots (P=0.0135) (Fig. 3) developed HI, in 18 and 17 months respectively (Table 2). The prognostic value for developing HI was P= 0.1410 for GS (Fig. 4). The time to disease progression to HI, stratified according to the PSA levels, the GS and BS, are shown in Figure 5. High initial serum PSA levels within the years of palliative hormonal treatment predicted the likelihood of progression to HI more than TNM staging, BS and GS.On the contrary, the combination of all risk factors studied increased prognosis related to HI (P<0.001) in our patients.

From our patients 6/40 (15%), died between 3 and 6 months while 26/40 patients (65%), had not progressed to HI during the follow-up period.

Table 2. *Multivariate analysis of risk factors for progression to hormone independency.*

TNM*	No (%)	Time to HI PCa (months)	P value
T_1-$T_2N_{0-1}M_{0-1}$	4 (29)	22	0.1410
T_3-$T_4N_{0-1}M_{0-1}$	10 (71)	15	
Gleason score			
≥ 7	10 (71)	12	0.043
< 7	4 (29)	20	
Bone scan (hot spots)			
$T_{1-4}N_{0-1}M_{0-Mb}$			
> 6	6 (42)	6	0.0135
< 6	8 (58)	17	
Initial PSA ng/ml			
≤ 50	10 (71)	23	0.002
> 50	4 (29)	18	
TNM & GS & BS & PSA			P<0.001
Disease progression			
HI - Pca (+)	14 (35)	2 years	
HI - Pca (-)	26 (65)		
Deaths	6 (15)	3-6 months	
Total	**40**		

* T3a-c: unilateral (a), bilateral extraprostatic (b) extension and invasion of seminal vesicles (c), T4a-b: invasion of bladder neck, rectum or external sphincter (a) and invasion of elevator muscle or pelvic floor (b). N1-3: lymph node metastasis and M1b: bone metastases.

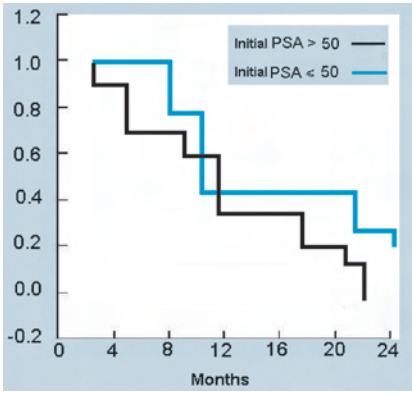

Figure 2. Time to disease progression according to the initial PSA. The grey line represents PSA levels < 50 ng/ml and the black one represents those patents with PSA levels > 50 ng/ml (P=0.002).

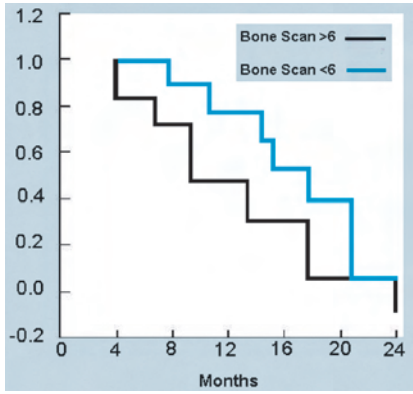

Figure 3. Time to disease progression according to the bone scintigraphy (BS) with less than three hot spots on a bone scan and more than 6 hot spots (P=0.135).

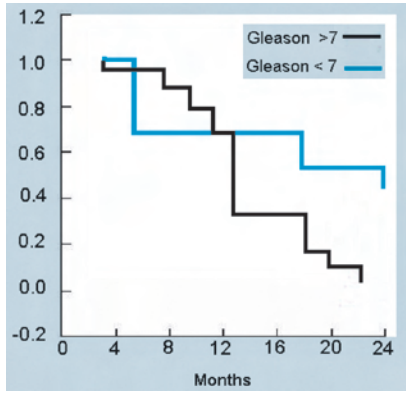

Figure 4. Time to disease progression according to the Gleason score of TRUS prostate biopsy. The grey line represents GS<7 and the black line, GS≥7 (P=0.043).

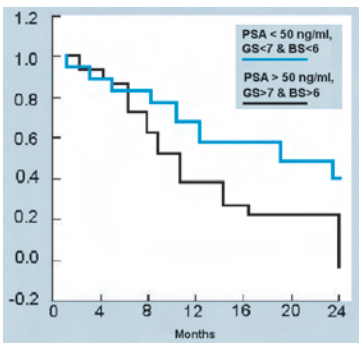

Figure 5. Time to disease progression according to the initial PSA, Gleason score of TRUS prostate biopsy and bone scan. In this plot the grey line represents PSA levels<50 ng/ml, GS<7 and with less than three hot spots on a bone scan. The black one represents those patents with PSA levels > 50 ng/ml, GS≥7 and more than 6 hot spots (P<0.001).

Discussion

PSA is a human kallekrein secreted by prostate epithelial cells as a normal component of the ejaculate. These cells are the progenitor cells of prostate adenocarcinoma [9]. The initial evaluation of patients with PCa after radical prostatectomy includes BS and PSA measurements [10, 21]. PSA monitoring in patients undergoing irradiation or anti-androgen treatment has been shown to be of prognostic value [21-24]. PSA is the most significant variable associated with the progression of PCa while the extent of bone metastases are shown in the BS [18-20]. After radical treatment, a rise in the PSA levels indicates the need to perform a bone scan [25]. When our patients had a PSA level of < 300 ng/dL and more than 6 areas of increased uptake on the BS their prognosis as indicated by the HI stage, was poor [26].

Since the ultimate value of any grading system is its prognostic ability, others have shown in a series of 2911 patients with subsequent follow up studies, that GS alone had a good correlation to prognosis [27]. It has been shown that biopsies with a high GS, combined with an elevated PSA level of >10 ng/ml are significant risk factors for extra capsular extension seminal vesicle and lymph node invasion [18].

BS in PCa is usually performed when PSA levels are above 10μg/L or in a T_3 stage or in a poorly differentiated PCa [28]. Other investigators underline the difficulty in assessing treatment outcomes for metastatic PCa because changes in bone scan are difficult to quantify and changes in PSA levels may not be associated directly with the effectiveness of treatment. A strong correlation between progression-free survival and overall survival could give an objective outcome with which to determine the efficacy of treatment methods in clinical trials. The same authors found that the relationship between radiographic progression-free survival events and overall survival events was the most weak for the early progression-free events. They further demonstrated that, in contrast with the relationship between PSA progression-free survival and overall survival this relationship became weaker in follow-up period. However, neither association was strong. These authors conclude that the clinical trial end point of progression-free survival may be problematic, especially for a stage of metastatic PCa [29].

To our knowledge, our study is the first to report the progression value to HI and survival rate of GS, initial serum PSA, TNM staging and BS in patients with advanced PCa under palliative hormonal treatment. Limitations of this study include the relatively small number of patients and the limited follow-up period.

In conclusion, according to the results of this study, the combination of TNM stage, initial serum PSA levels, GS and BS upgraded the prognostic value to HI of our patients (P<0.001). Although no other study has shown that this combination improves prognosis for the development of metastases, it is of importance to predict HI and thus select appropriate additional treatment.

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