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# Characterizing the Medical Pertinence for the Indication of a Bone Scan by Urologists, in Patients with Prostate Cancer

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**Abstract:** *Introduction*: Prostate cancer (PC) is the second most frequently diagnosed tumor in men, and bone scan (BS) is one of the diagnostic images used for staging and follow-up. Precise indications for performing a BS exist and an overuse of this diagnostic modality is suspected. It is relevant to evaluate the medical pertinence when requesting a BS to promote self-regulation, protect the health system and reduce radiation doses. *Methods*: This is a descriptive, retrospective study. Medical records of patients with PC diagnosis were reviewed. We included patients evaluated by a urologic oncologist at the outpatient scenario, at San Ignacio Hospital, Bogotá, Colombia, in the second trimester of 2019. Epidemiological and staging data were recorded for each patient, as well as the number of BS requested, the type of BS performed, the PSA at the time of performance and the impact of the result on medical decisions. Clinical indications for requesting a BS were classified, according to RADAR III guidelines. An analysis was performed using Excel (measures of central tendency and frequency). *Results*: A total of 234 patients were evaluated (mean age: 74.47 years; mean follow-up time: 32.3 months). At least one BS was requested in 55% of patients (mean 1.54), with a total of 199 BS performed. The most frequent indication for a BS was PSA progression in patients with androgen deprivation therapy (ADT), in hormone-sensitive prostate cancer (31%). 18% of the requested BS could have been omitted (inappropriate indication). The mean PSA at performance for BS that showed bone metastasis (33%) was 151.27ng/ml and 19.75ng/ml for those negative (67%). Medical behavior was not impacted by the result of any of the BS that didn´t have an appropriate indication according to the established guidelines, but it was affected by 85% of those correctly requested. *Discussion and Conclusions*: BS is a conventional image that it widely performed for the staging and follow-up of PC. There are precise indications according to the NCCN and RADAR III guidelines for performing one in a PC patient. It was observed that with some frequency it is requested unnecessarily, without having any impact on the clinical decisions for the patient. The relevance of medical self-regulation and knowledge of scientific evidence are highlighted to prevent unnecessary exposure to radiation, optimize the impact of the results of these tests on clinical behavior and protect the health system.

**Keywords:** Bone Scan, Medical Pertinence, Prostate Cancer

## 1. Introduction

Prostate cancer (PC) is the second most frequently diagnosed tumor in men; with an incidence of 33 new cases per 100,000 habitants in 2018 and a prevalence of 27.5% for this same year according to the Global Cancer Observatory (GLOBOCAN, 2018) [1, 2]. In an autopsy study, a prevalence of more than 50% was reported in patients over 79 years of age [3]; according to the *Cuenta de alto costo* (2018), in Colombia in 2017 there were 25,623 new cases of OC in the country, with a median age of presentation of 73 years [4].

Being such a prevalent pathology, research in this field provides a variety of therapeutic options that depend directly

on the staging of cancer [1]. At our institution, medical decisions are guided according to the NCCN guidelines (National Comprehensive Cancer Network), in which patients are classified into risk groups, according to histology, digital rectal examination (DRE) and the Prostate Specific Antigen (PSA) – very low risk, low risk, favorable intermediate risk, unfavorable intermediate, high risk and very high risk – [5]

According to this classification, the indication for staging imaging studies is determined; conventional images such as the bone scan (BS) and contrasted computed tomography (CT) are frequently performed with this purpose [5, 6].

The BS has been the imaging modality most widely used to evaluate bone metastases in patients with PC. A meta-analysis published in 2014 (Shen, et al.) showed that the sensitivity and specificity for the detection of bone metastases per patient was 79% (95% CI, 73%-83%) and 82% (95% CI, 78%-85%) respectively, with an area under the curve (AUC) of 0.8876 [7]. This has been more recently reassessed; in the same meta-analysis (Shen, et al.) better sensitivities and specificities, as well as AUC are reported for MRI (magnetic resonance imaging) and PET/CT (Positron Emission Tomography). However, the BS remains a sensitive and specific, but more important, accessible study that allows for the staging and follow-up of PC patients [7].

There are groups such as RADAR III (Radiographic assessments for detection of advanced recurrence), that aim to precisely establish the indications for the performance of conventional imaging studies such as BS and CT, as well as new generation imaging studies such as PET-CT, in the early diagnosis of bone metastases in the PC, according to the available clinical evidence [6]. Likewise, the NCCN guidelines propose the scenarios in which to consider the BS [5].

When verifying in detail the proposed algorithms, observations and special situations are found in which the urologist may or may not consider requesting the BS, and therefore it is suspected that there may be variability in the clinical consideration when indicating one in urological practice. It becomes relevant for the country and for the health system to evaluate and describe the medical pertinence and reasonable use of studies and resources, as well as to evaluate the current benefit of requesting the imaging study in each patient in order to promote self-regulation in physicians, protect the Colombian health system and reduce radiation doses in each patient.

Considering this, the objective of this paper is to characterize the indications, pattern of use and request of bone scan in patients with prostate cancer in a fourth level institution in Bogotá, Colombia.

# 2. Methods

### *2.1. Type of Study*

This is a descriptive, retrospective observational study.

### *2.2. Inclusion Criteria*

We included patients diagnosed with PC, evaluated by a urologic oncologist at the outpatient scenario at the San Ignacio Hospital (Bogotá, Colombia) in the second quarter of 2019. Patients who had a BS performed outside the institution or who had an incomplete medical history were excluded.

### *2.3. Variables*

A rigorous review of the medical history was carried out from the first assessment in the institution by a urologic oncologist, until the last assessment at the institution. The following variables were registered:

Age (in years) at the time of assessment; the initial tumor staging including the initial PSA (last PSA in ng/ml before biopsy), Gleason Score Group documented in the biopsy (Group 1 (Gleason 3+3), Group 2 (3+4), Group 3 (4+3), Group 4 (4+4, 5+3), Group 5 (4+5, 5+4, 5+5), DRE – T1 (Non-palpable disease), T2 (palpable disease), T3 (Extra prostatic disease), T4 (adjacent structures) – and finally, the risk group according to NCCN (5).

Also, we reviewed whether they had received any type of treatment outside the institution prior to the first institutional assessment and what type of treatment, as well as the follow-up time in months (from the first to the last assessment by urologic oncology).

Within this follow-up time, we recorded how many BS had been requested for each patient, the type of BS performed – with or without single photon emission tomography (SPECT) – and which specialty requested it (Urology, Oncology, Radiotherapy or Orthopedics).

Also, the clinical indication for which the BS was requested and whether this indication was appropriate according to the information in the medical history was specified. Additionally, whether the BS was positive or not for metastatic disease and whether the result had any impact on clinical behavior (defined as any change in treatment according to the outcome of the BS). Finally, the PSA value in ng/ml at which each BS was requested and taken was recorded.

### *2.4. Clinical Indications for a Bone Scan*

To determine the indications and verify the pertinence of the BS, the RADAR III group [6] guidelines, described below for the different scenarios, were considered:

#### *2.4.1. In Patients with De-novo PC Diagnosis*

In intermediate and high-risk groups according to the NCCN, who have PSA greater than 10ng/ml, Gleason greater than or equal to 7 or palpable disease (greater than or equal to T2b). In this group of patients, new generation images should only be requested if there is a high suspicion of metastatic disease and conventional images are negative or misleading.

#### *2.4.2. In Patients with Biochemical Recurrence or Relapse*

When PSA is between 5 and 10 ng/ml. If negative, follow-up should be performed with a second image when the PSA is equal to or greater than 20 ng/ml and then each

PSA duplication based on quarterly monitoring. Only new generation images should be requested in PSA greater than or equal to 0.5 ng/ml.

#### *2.4.3. In Patients with Non-metastatic Castration Resistant Disease (nmCRPC)*

When the PSA level is greater than or equal to 2 ng/ml. If negative, when the PSA is greater than or equal to 5 ng/ml and subsequently each PSA duplication based on quarterly monitoring. A new generation image should only be considered in the scenario of a doubling time of less than 6 months, when the patient benefits from therapies for metastatic castration resistant disease (mCRPC).

#### *2.4.4. In Patients with mCRPC*

Always use conventional images for diagnosis and follow-up, if negative, consider new generation images. The indication is each duplication of PSA from the previous image, every 6-9 months with stable PSA, with changes in symptomatology or with changes in general status.

### *2.5. Statistical Analysis*

After data collection, descriptive statistics were used for continuous variables with measures of central tendency (means and ranges). For categorical variables, frequency measurements were used with the use of proportions.

## 3. Results

### *3.1. General Population*

A total of 234 patients evaluated over a three-month period were included for data analysis, with a mean age of 74.47 years (range 51-96) and a mean follow-up time of 32.3 months (range 1-174).

Initial staging (See Table 1) showed a mean initial PSA of 79.95 ng/ml (range 0.67-1603 ng/ml); the initial Gleason Score Group 1 was the most frequent (30.8%), as well as T2 disease on DRE (36.8%) and high-risk disease according to the NCCN guidelines (28.6%). Any kind of treatment - prior to assessment at the institution – was received by 43.6%, with ADT for HSPC being the most frequent treatment (45.1%).

### *3.2. Bone Scans Indicated*

Of the 234 patients evaluated, at least one BS was indicated in 55% (129 patients) within the follow-up time (mean 1.54; range 1-6), for a total of 199 BS requested (See Table 2). Of the 105 patients (45%) who did not have any BS requested during the follow up, 10% (11 patients) had a clinical indication for performing one.

The most frequent reason for requesting a BS was PSA progression in patients treated with ADT in HSPC (31%), followed by staging at initial diagnosis (28%). Of the BS requested, 36 of them (18%) didn't have an appropriate indication according to the guidelines; these non-pertinent requests were more often justified because of PSA progression in patients with ADT in HSPC (17 BS)".

***Table 1.*** *General population.*

| | | |
|---|---|---|
| Total of patients analysed (n/%) | 234 | 100% |
| Age in years (mean/range) | 74,47 | (51-96) |
| Follow-up in months (mean/range) | 32,3 | (1-174) |
| Initial PSA ng/ml (mean/range) | 79,95 | (0,67-1603) |
| Initial Gleason Group (n/%) | | |
| Unknown | 37 | 15,8% |
| 1 | 72 | 30,8% |
| 2 | 55 | 23,5% |
| 3 | 24 | 10,3% |
| 4 | 31 | 13,2% |
| 5 | 15 | 6,4% |
| Initial staging (n/%) | | |
| T1a-b | 7 | 3,0% |
| T1c | 50 | 21,4% |
| T2a-c | 86 | 36,8% |
| T3a-b | 28 | 12,0% |
| T4 | 19 | 8,1% |
| Tx | 44 | 18,8% |
| NCCN Risk Group (n/%) | | |
| Very low risk | 22 | 9,4% |
| Low risk | 20 | 8,5% |
| Intermediate favorable risk | 31 | 13,2% |
| Intermediate unfavorable risk | 14 | 6,0% |
| High risk | 67 | 28,6% |
| Very high risk | 8 | 3,4% |
| Regional | 2 | 0,9% |
| Metastatic | 25 | 10,7% |
| Unknown | 45 | 19,2% |
| Previous treatments (n/%) | | |
| Any treatment | 102 | 43,6% |
| Observation | 1 | 1,0% |

| | | |
|---|---|---|
| Total of patients analysed (n/%) | 234 | 100% |
| Age in years (mean/range) | 74,47 | (51-96) |
| Follow-up in months (mean/range) | 32,3 | (1-174) |
| Initial PSA ng/ml (mean/range) | 79,95 | (0,67-1603) |
| Initial Gleason Group (n/%) | | |
| Active surveillance | 1 | 1,0% |
| Radical prostatectomy + Pelvic lymphadenectomy | 24 | 23,5% |
| Radical prostatectomy | 7 | 6,9% |
| Radiotherapy + ADT | 9 | 8,8% |
| Radiotherapy | 9 | 8,8% |
| ADT for HSPC | 46 | 45,1% |
| ADT for nmCRPC | 0 | 0,0% |
| ADT for mCRPC | 5 | 4,9% |

HSPC: hormone-sensitive prostate cancer; nm: non-metastatic; m: metastatic; CRPC: castration resistant prostate cancer; ADT: androgen deprivation therapy

***Table 2.*** *Bone Scans indicated.*

| | | | | |
|---|---|---|---|---|
| Total of patients analysed (n/%) | 234 | 100% | | |
| Patients with no BS (n/%) | 105 | 45% | | |
| But did have an indication (n/%) | 11 | 10,40% | | |
| Patients with at least one BS (n/%) | 129 | 55% | | |
| Number of BS indicated per patient (mean/range) | 1,54 | (1-6) | | |
| Total BS indicated (n) | 199 (100%) | | | |
| Clinical indication (n/%) | Total | | Wrong indication | |
| *de-novo PC diagnosis* | 55 | 28% | 3 | 1,5% |
| *Biochemical recurrence or relapse* | | | | |
| Post-RP | 26 | 13% | 6 | 3,0% |
| Post-RT | 9 | 5% | 4 | 2,0% |
| Post-ADT | 61 | 31% | 17 | 8,5% |
| Symptoms | 22 | 11% | 2 | 1,0% |
| *nmCRPC* | | | | |
| According to PSA value | 6 | 3% | 2 | 1,0% |
| Symptoms | 1 | 1% | 0 | 0,0% |
| *mCRPC* | | | | |
| According to PSA value | 19 | 10% | 2 | 1,0% |
| Total | 199 | 100% | 36 | 18,1% |

BS: bone scan; PC: prostate cancer; RP: radical prostatectomy; RT: radiotherapy; ADT: androgen deprivation therapy; nm: non-metastatic; m: metastatic; CRPC: castration resistant prostate cancer

### *3.3. Characterization and Results of the Bone Scans*

Most of the requested BS were performed without SPECT (58%) (See Table 3); the PSA at the time of the BS request was on average 62.7 ng/ml (range 0-2184). Of the BS requested, 33% showed metastatic disease; in this group, the mean PSA at the time of performance was 151.27 ng/ml; in contrast to 19.75 ng/ml in the group of BS with negative result (67%). Finally, 85% (n=169) of the requested BS had an impact on clinical behavior (96% of these correctly indicated); in contrast, of the 15% of the BS that had no impact on the behavior (n=30), 100% were not pertinent according to the established indications in guidelines.

## 4. Discussion and Conclusion

PC has a high prevalence and incidence in the world population [2, 8] and BS is one of the most frequently used diagnostic images in the staging and follow-up of this disease, whit the purpose of identifying the presence of bone metastases [9].

It has been observed that the PSA level correlates directly with the positive or negative result of BS [10] and RADAR III guidelines consider the absolute value of PSA to indicate a BS in each clinical scenario [6]. A 2018 meta-analysis (Suh, et al.) that included 54 studies, involving 20,421 HSCP patients, found a cumulative proportion of positive BS for PSA less than 10 ng/ml of 3.5% (95% CI, 5.1-10.6%), for PSA 10-20 ng/ml of 6.9% (95% CI, 4.5-10-3%) and for PSA greater than 20 ng/ml of 41.8% (95% CI, 36.3 – 47.6%), with a statistically significant difference ($p<0.0001$) [11]. Although ours is a descriptive study, it can be observed that the mean PSA at the time of the request of the BS that were positive, was higher than that of the BS that were negative, which is directly correlated with what was described in the literature.

Regarding the type of BS requested, it has been documented that the addition of three-dimensional information (SPECT) to the BS maintains the sensitivity and improves the specificity of the study; in some reports, it becomes similar to that of the MRI and CT [12, 13]. In the patients evaluated in our study, the type of BS requested was most frequently without SPECT, however, there is a tendency to increasingly request BS with SPECT, considering that it has a better diagnostic performance.

As an important finding of our analysis, it was documented that in a follow-up time of about 32 months at least one BS was requested in more than half of the patients evaluated and some had up to 6 BS in the follow-up time, so it becomes

important to evaluate the pertinence of the indications for this diagnostic tool.

The NCCN guidelines [5] and the RADAR III consensus [6] clearly establish the indications for a BS in the initial staging and clinical follow-up of patients with PC. According to the evidence reviewed, a BS should be requested in the staging of unfavorable intermediate-risk, high-risk and very-high-risk disease, but it is not indicated in localized low-risk/very-low-risk or favorable intermediate-risk disease. Another scenario is in the follow-up of the patient after radical prostatectomy who presents a biochemical relapse or persistence of PSA in the postoperative period, also in the post-radiotherapy patient with a progressive rise in PSA in symptomatic patients and finally, in the progression of PSA in patients with advanced disease in ADT (castration resistance) [5, 6]

Considering these criteria, an analysis of each BS requested in the evaluated patients was performed. It was found that, in the general population, a BS was requested mainly in the post-treatment clinical follow-up scenario (post-ADT), followed by the initial staging scenario. It is of great relevance to highlight that a BS was indicated without meeting the previously mentioned criteria in 18% of the cases (See Table 2), mainly because the BS was performed with very low PSA values [6].

Accordingly, we documented that the result of the BS that were non-pertinent had no impact on treatment in any of the cases; in contrast, of the BS requested with an appropriate indication, there was an impact in the medical decision for most cases. This becomes relevant because according to Colombia's Statutory Law 1751 of 2015, which establishes that health is an autonomous fundamental right, the health professional is also autonomous to make clinical decisions, based on the principles of self-regulation, ethics, rationality and most importantly, the available scientific evidence [14].

***Table 3.*** *Characterization and results of the Bone Scans.*

| **Total BS indicated (n)** | **199 (100%)** | |
|---|---|---|
| Type of BS | | |
| *Without SPECT* | 115 | 58% |
| *With SPECT* | 84 | 42% |
| PSA value at performance of BS ng/ml (mean/range) | 62,72 | (0-2184) |
| Metastasis (n/%) | | |
| *Yes* | 65 | 33% |
| Mean PSA (ng/ml) | 151,27 | |
| *No* | 134 | 67% |
| Mean PSA (ng/ml) | 19,75 | |
| Impact on clinical behaviour (n/%) | | |
| *Yes* | 169 | 85% |
| Correct indication | 163 | 96% |
| Wrong indication | 6 | 4% |
| *No* | 30 | 15% |
| Correct indication | 0 | 0% |
| Wrong indication | 30 | 100% |

SPECT: single photon emission tomography

This point is of crucial relevance, because it implies that the physician has autonomy when making diagnostic and therapeutic decisions but trusts that the clinician must have the scientific knowledge and the ability to self-regulate and prioritize the indicated behaviors, in order to optimize resources and protect the health system but guaranteeing optimal medical care to the patient [15].

Additionally, despite being a tool with great diagnostic performance, the BS is a diagnostic image that involves irradiation for the patient. The effective radiation dose is a measure that allows to approximate the effect of radiation on the body, and it has been documented that a BS has an effective dose of 6.3 mSV, compared to the annual radiation of the environment that is around 3 mSV [16].

In relation to the aforementioned, this analysis becomes relevant because it is important to feed back the physicians and encourage them to constantly reevaluate their medical pertinence as well as to keep up with the last scientific evidence in order to reduce the extra costs to the health system, radiation to the patient and optimize medical care and health system resources.

In conclusion, the BS is a frequently requested study in the staging and follow-up of patients with PC in our series. We observed a low impact on clinical behavior when the BS was requested outside the indications proposed by the guidelines. It should be emphasized that the medical indication adheres to the guidelines in order to minimize radiation exposure and optimize the impact of the results on clinical behavior.

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