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Risk factors associated with metastasis in patients with prostate cancer. A single-center observational study

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Abstract

Introduction: Prostate cancer (PC) is the second most common cancer diagnosed in men, with the highest incidence at 66 years of age. Obesity, smoking, alcoholism, and a family history of PC are associated with the risk of metastasis. This study aimed to measure the association between factors and the met- astatic state in patients with PC in a single reference center in Ecuador.

Methodology: This analytical study was conducted at the "Teodoro Maldonado Carbo" Hospital in Guayaquil-Ecuador, January-December 2019. The sample calculation was nonprobabilistic, census type, and cases with PC were included. The variables were age, PSA, Gleason score, presence of metastases, symptoms, smoking, obesity, and history. The odds ratio was used to measure the association with a 95% confidence interval and P value.

Results: The study included 363 patients, with a mean age of 75.2 ± 9.6 years. The group with metastasis included 202 patients (55.65%). Bone metastasis 32.5%, lung 9.6%, lymph nodes 8.8%, and liver 4.75%. In the symptomatology, the most frequent were dysuria (44.4%), 33.6% with pollakiuria, 13.2% hematuria, and 8.8% tenesmus. Gleason stage-9 OR=24.85 (95% CI 1.47-419.8) *P* =0.0259. PSA level >19 ng/ml OR=
6.996 (95% CI 2.68-18.29) *P* =0.0001. Smoking OR=2.34 (95% CI 1.52-3.60) *P* =0.0001. Protective factors
were PSA value <19 ng/ml OR=0.082 (95% CI 0.043 -0.157) P<0.0001, arterial hypertension consultation OR=0.33 (95% CI 0.161-0.691) *P* =0.0032 and stage Gleason-6 OR=0.108 (95% CI 0.0665-9.1736) *P*
<0.0001.

Conclusion: PSA levels >19 ng/ml and Gleason stage > nine are associated with metastases in patientswith PC.

Keywords:
MESH: prostate neoplasms, prostate-specific antigen, neoplasm metastasis, risk factors, relative odds.
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Introduction

Prostate cancer is the second most diagnosed cancer in men worldwide, with the highest average incidence at age 66 [1]. In developed countries, prostate cancer is diagnosed at earlier ages when it is confined to the prostate gland due to the use of prostate-specific antigen (PSA) [2]. The specific prostate antigen is a protein created by the prostatic epithelium that is specific to the organ but not to cancer because it can be elevated in pathologies such as prostatitis and benign prostatic hyperplasia, among others. However, it is the best biomarker thus far for the early diagnosis of prostate cancer.

According to the American Academy of Family Physicians, 3 out of 10 men with elevated PSA have a high risk of suffering from prostate cancer, which will depend on age and the PSA level found. Some studies show that routine PSA tests in men between 55 and 66 significantl y reduce mortality from prostate cancer. However, the test's low specificity for prostate cancer makes its interpretation inconclusive [3].

The Gleason Scale is a grading system used once the diagnosis of prostate adenocarcinoma has been established to measure the histopathological aggressiveness of the neoplasia [4]. It is fully established that the Gleason score, according to the histopathological findings of the tumor, allows us to categorize patients more precisely and thus have a clear idea of the patient's prognosis.

With this background, the objective was to determine the risk factors associated with metastasis in patients with prostate cancer in a regional reference center in Guayaquil, Ecuador.

Materials and methods

Study design

The present study is observational-analytic. The source is retrospective.

Study area

The study was carried out in the urology service of the "Teodoro Maldonado Carbo" Specialties Hospital of the Ecuadorian Institute of Social Security in Guayaquil-Ecuador. The study period was from January 1, 2019, to December 31, 2019.

Universe and scenery

The universe was made up of all patients registered in the institution. The sample size calculation was nonprobabilistic, census type, where all incident cases in the study period were included.

Participants

Cases of adult patients diagnosed with prostate cancer in whom PSA assessment and the Gleason scale were available were included. Incomplete records were excluded from the analysis.

Variables

The variables were age, PSA, Gleason scale, presence of metastases, symptoms, and diagnostic methods.

Procedures, techniques, and instruments.

The data were collected from the clinical history in a form designed exclusively for this purpose. PC diagnoses were made by ultrasound-guided fine needle aspiration (FNA). Different pathologists read the plates. The AS400 system was used to search for cases using the coded diagnosis: C61.

Avoidance of bias

To guarantee the reliability of the information, the researchers were trained in data collection. A double checklist was used to include the cases. The data were validated and cured by the principal investigator.

Statistical analysis

Once the information was compiled in an Excel spreadsheet, it was entered into a data matrix of SPSS™ 22.0 software (IBM, Chicago, USA). Descriptive statistics were used based on frequencies and percentages for the qualitative variables and the quantitative measures of central tendency. The odds ratio was used as an association measure with a 95% confidence interval and P value.

Results

The study included 363 patients.

Clinical characterization

There were 363 patients, with a mean age of 75.2 ± 9.6 years. The minimum age was 49 years, and the maximum was 98 years.

There were 202 patients with metastases (55.65%). Regarding the place of metastatic spread, a greater predilection to develop bone metastasis was found in 32.5% of the patients, followed by pulmonary metastasis in 9.6%, lymph node metastasis in 8.8%, and liver metastasis in 4.75% of the cases. The most frequent symptomatology was dysuria (44.4%), followed by pollakiuria (33.6%), hematuria (13.2%), and tenesmus (8.8%). The most systematic study used was prostate echo, with 42.7%; tomography, 20.4%; prostate scintigraphy, 25.6%; and magnetic resonance imaging, with 11.3%.

Clinical factors

A total of 44.4% of the patients suffered from alcoholism, 27.5% presented smoking, 23.1% were meat and dairy consumers, 4.7% reported other infrequent habits, and 0.3% did not refer to any habit of importance. Within the pathological antecedents, it was evidenced that 54.5% of the patients had a family history of prostate cancer, 29.2% presented obesity and over- weight, in third place, with 9.9% of the patients suffering from arterial hypertension, and among other associated antecedents, they had a percentage of 5.5% (Table 1).

Of all those evaluated, 45.2% had Gleason 6, while those with values on the Gleason Scale of10 reached 1.4%.

Risk measurement is presented in Table 1. Risk factors for the development of metastases were smoking and Gleason clinical stages 7, 8, and 9, with PSA values in ranges of 19-49 ng/ml, 50 to 99 ng/ml, and 100-299 ng/ml. Statistically significant protection factors were established as a personal history of benign prostatic hyperplasia, arterial hypertension, Gleason 6 clinical stage, and PSA value <19 ng/ml (Table 1).

Table 1. Factors associated with metastasis in prostate cancer

	Metastasis N=202	No metastases No.=161	OR		
			OR	95% CI	*P*
Smoking	108 (53.5%)	53 (32.9%)	2.3412	1,524-3,597	0.0001
Alcoholism	58 (53.7%)	42 (26.1%)	1.1412	0.717-1.818	0.5781
PPH: HPB	0 (0%)	1 (0.6%)	0.0093	0.0006-0.1527	0.0010
FPH: Ca Prostate	116 (57.4%)	82 (50.9%)	1.2995	0.8570-1.9704	0.2174
Overweight/Obesity	59 (29.2%)	47 (29.2%)	1.0007	0.6347-1.5780	0.9974
AHT	12 (5.9%)	24 (14.9%)	0.3333	0.161-0.691	0.0032
Gleason 6	46 (22.8%)	118 (73.3%)	0.1075	0.0665-0.1736	<0.0001
Gleason 7	99 (49.0%)	39 (24.2%)	3.0067	1.9096-4.7343	<0.0001
Gleason 8	38 (18.8%)	3 (1.9%)	12.2033	3.6919-40.337	<0.0001
Gleason 9	14 (6.9%)	0 (0%)	24.8462	1.4706-419.80	0.0259
Gleason 10	5 (2.5%)	0 (0%)	8.9949	0.4937-163.89	0.1380
PSA <19 ng/mL	102 (50.5%)	149 (92.5%)	0.0821	0.0429-0.1573	<0.0001
PSA 19-49 ng/ml	37 (18.3%)	5 (3.1%)	6.9964	2.6810-18.258	0.0001
PSA 50-99 ng/ml	34 (16.8%)	5 (3.1%)	6.3143	2.4087-16.553	0.0002
PSA 100-299 ng/ml	19 (9.4%)	2 (1.2%)	8.2541	1.8932-35.988	0.0050
PSA 300-499 ng/ml	5 (2.5%)	0 (0%)	8.9949	0.4937-163.90	0.1380
PSA >500 ng/mL	5 (2.5%)	0 (0%)	8.9949	0.4937-163.90	0.1380

PPH: personal pathological history. FPH: Family pathological history. BPH: benign prostatic hyperplasia. Ca: Cancer. PSA: prostate-specific antigen. OR: Odds ratio. CI: confidence interval. AHT: Arterial hipertensión.

Discussion

When comparing this study with previous research, it was found that age constitutes a non-modifiable risk factor for prostate cancer. According to the National Cancer Institute in the United States, in its Surveillance, Epidemiology, and Outcomes (SEER) statistical program in 2015-2019, a higher incidence of cases was found in patients who were between 70-74 years of age [5], as was also described by the work of Leitzmann et al. in the years corresponding to 2000-2008, where the incidence began to increase from 40-44 years of age to reach its maxi- mum peak of 984.8 patients per 100,000 men aged 70-74 years [6]. Similarly, in this study, the minimum age was 49 years in the population with a maximum of 98 and an average of 75.15. Regarding the distribution of anatomical regions where metastasis usually occurs in prostate cancer, bone (84%) was determined, distant lymph nodes (10.6%) and liver (10.2%) [7] according to a study conducted by Gandaglia et al., similar to this study, the most frequent site was at the bone level with 32.5% of all patients, followed by pulmonary metastasis with 9.6% and lymph node metastasis with 8.8%. In turn, Auz and Brito (2018) found in their re-

search carried out at the Hospital Solca Núcleo de Quito-Ecuador, which included 1713 patients, where the most frequent site of metastasis was bone in 82.25%, followed by lymph nodes with 7.05% and then 2.8% at the lung level [8].

Regarding the habits of patients, 44.4% of the patients in this study consumed alcohol regularly. In comparison, 27.5% consumed tobacco, and 23.1% were consumers of meat and dairy products, which contrasts with the study of Auz and Brito (2018) previously detailed, where 31.1% of the patients consumed alcohol regularly, and 28.3% of the patients used tobacco at the time of diagnosis. Data were not measured concerning the consumption of dairy products and red meat [8].

A significant nonmodifiable risk factor was the presence of a family history of prostate cancer in this study with 54.5% of the patients; in the work of Auz and Brito (2018), only 9% had a family history of prostate cancer and 23.2% of other types of cancers [23]. According to Barber et al., patients with a family history of prostate cancer only have a 68% increased risk of suffering the same (95% CI 1.53-1.83) and a 72% risk of fatal disease [9]. This increased risk was also described by Powell IJ (2011) in his publication, which says that men with first-de- gree relatives (father, brother, son) have a risk of developing prostate cancer that is approximately double that of the general population [10].

In the present study, 29.2% of the patients were overweight, and 9.9% of the patients had arterial hypertension. Likewise, in the study by Möller et al., it was found that a high BMI (26) compared to 20-22 at the age of 21 years was associated with a lower risk of lethal or advanced prostate cancer and Gleason 7 [11]. There is also talk about which of the components of the syndrome metabolism, including arterial hypertension, none is related to the development of prostate cancer [10].

Dysuria was found among the most frequent symptoms in this study, with 44.4% of all patients, followed by frequency (33.6%) and hematuria (13.2%). Similarly, the study by Birtle et al. carried out between 2000 and 2001 with databases of the British Association of Urological Surgeons determined that of 33 patients with metastatic prostate cancer with PSA <10 ng/ml, 51% presented with urinary symptoms and pelvic pain, 21% had bone pain, 18% had urinary retention, and 10% had cachexia in Malaysia [12].

In the present study of all the patients, 45.2% of them had Gleason scores of 6, and to a lesser extent, 1.4% of the patients had Gleason scores of 10; this can be compared with the study by Thomsen et al., where it was found that high scores on the Gleason scale were related to the presence of metastasis; thus, in that study, 41% of the patients who presented distant metastases according to the TNM scale (M1) had a Gleason score of 5. In comparison, only 3% had Gleason 1 [13].

The imaging method most commonly used in this study was prostate ultrasound (42.7%) and, to a lesser extent, magnetic resonance imaging (11.3%). In the research by Huang et al., it was found that the use of MRI with the PI-RADS v2 system was the most accurate system to predict metastasis to lymph nodes in the pelvic area, and patients with PI-RADs <5 were associated with a shallow risk of nodal metastasis [14]. 3D prostate ultrasound demonstrated 84% sensitivity and 96% specificity to identify macroscopic extracapsular tumor extension and was able to identify 14/16 disseminations to the seminal vesicle, according to Mitterberger et al. in 2008 [15]. Finally, for PSA values that occurred in patients diagnosed with prostate can- cer, it was possible to show that 100% of patients with PSA more significant than 500 ng/ml had metastasis, as well as the group of patients with 300- 499 ng/ml PSA, unlike the group

with less than 19 ng/ml PSA where only 40.6% had metastases, which can be compared to the study by Thomsen et al. where of the patients with more than 400 ng/ml, 64.9% presented metastases, followed by the group with values of 200-399 ng/ml where 54% developed metastases and finally the group with less than 19 ng/ml had In only 1.45% of patients with metastasis, we can thus deduce that the PSA value is directly proportional to the risk of metastasis; however, we recommend taking more risk factors into account for a comprehensive evaluation of the patient [13].

Conclusions

In order of statistical importance, the factors associated with metastasis in prostate cancer are Gleason clinical stage 9 and 8, PSA levels between 50 and 299 ng/ml, and smoking. Protective factors were a clinical history of benign prostatic hyperplasia, hypertension, and a PSA level <19 ng/ml.

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Administrative information

Abbreviations

PPH: personal pathological history.
FPH: Family pathological history.
BPH: benign prostatic hyperplasia.
Ca: Cancer.
PSA: prostate-specific antigen.OR: Odds ratio.
CI: confidence interval

Additional Files

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Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

Author contributions

Emily Gabriela Chimbo Acuña: conceptualization, validation, visualization, methodology, project management, writing: review and editing.

Karen Gabriela Valverde Zambrano: conceptualization, data curation, formal analysis, fundraising, research, resources, software, writing - original draft.

Iván Altamirano: conceptualization, data curation, formal analysis, fundraising, research, resources, software.

All authors read and approved the final version of the manuscript.

Ethics committee approval

It does not apply to studies of databases or medical records.

Consent for publication

The present study is a database analysis; it does not apply to this type of study.

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