Epidemiological, Pathological and Statistical Analysis of Penis Cancer in Espírito Santo - Analysis of 79 Cases.

Silva Júnior NF[1], Bechara GR[1*], Dettoni JB[1], Milagres MM[1], Da Rocha WS[1], Borges CF[1].

Department of Urology, Federal University of Espírito Santo, Vitória, ES, Brazil.

Purpose: To determine the epidemiological and pathological characteristics of penile cancer (PeCa) and to verify the independence between two statistical variables of patients with PeCa treated at the Urology Service of the Cassiano Antônio de Moraes University Hospital (HUCAM), Vitória, ES, Brazil .

Patients and Methods: Between 2010 and 2020, 79 patients with histologically confirmed PeCa were evaluated in our institution considering age, birthplace, ethnicity, marital status, practice of circumcision, histological type, growth pattern, site of tumor, tumor size, grade tumor, Chaux index, vascular invasion, lymphatic invasion, perineural invasion and pathologic stage (TNM staging). For the statistical treatment of square-data with p-value by Monte Carlo statistical calculations, in order to verify the independence between two variables, being the following: Degree of Pathological - TNM, Chaux Index, Lymphatic Invasion, Vascular Invasion and Perineural Invasion, with the patient's race and age group.

Results: The ages ranged from 25 to 87 years, with an average of 62 years. Of the 79 patients, 36 (45,56%) were from the metropolitan region, 07 (8,86%) were from the north, 14 (17,72%) were from the northwest and 22 (27,86%) from the south of the Espírito Santo state. Most patients were brown 45 (56,96%), married 51 (64,55%) and had not completed primary school 59 (74,68%). Of the 79 patients, only 4 (6,32%) circumcised. Grade I tumors were present in 35 (44,30%) of the patients, grade II in 32 (40,50%) and grade III in 10 (12,65%). Vascular invasion was observed in 13 (16,45%) and lymphatic in 7 (8,86%) patients. Regarding Chaux Index, 16 patients (20,25%) had Index 2, 19 (24,05%) had Index 3, 13 (16,45%) had Index 4, 19 (24,05%) had Index 5, 9 (11,39%) had Index 6, 1 (1,26%) had Index 7 and 2 (2,53%) were not evaluated. Of the total, 20 (25,31%) had corpora cavernosa and 24 (30,37%) corpus spongiosum

infiltration. According to the statistical analysis, there is evidence to reject the null hypothesis, that is, vascular invasion is related to the patient's age group, as p-value = 0.00449 < p-value =0.05.

Conclusion: Considering that the majority of penile cancer cases in the state of Espírito Santos are treated at the Department of urology of HUCAM, it can be concluded hat all patients in the study were residents of the state of Espírito Santo and had a low socioeconomic status. Most were brown hemones, married with low schooling and an average age of 62 years. The majority of cases have already been diagnosed with advanced disease. And after performing the chi-square tests and calculating the p value, we were able to conclude with statistical significance ($p<0.05$) the relationship between age group and vascular invasion, which may justify a worse prognosis the more the age group.

Key words: penile cancer; epidemiology; risk factors.

INTRODUCTION

Penile carcinoma (PeCa) is a rare malignant tumor, accounting for < 1% of male cancers in Europe and North America. On the other side, PeCa accounts for 10%-20% of malignant tumors in developing countries [1,2].

Squamous cell carcinoma (SCC) is the most common malignant lesion of the penis and there are several subtypes of penile SCC with different natural history. Penile SCC usually originate from the epithelium of the inner foreskin, glans, or coronal sulcus (approx. 90%) and less common on the penile shaft [3].

The etiology of penile SCC is multifactorial characterized by an increased incidence with age, with a peak in the sixth decade but it does occur in younger men. It is related to the socioeconomic conditions such as the lack of hygiene and preventive health care as well as phimosis, infection with high-risk human papillomaviruses (hrHPV), smoking, and chronic inflammatory states [4,5,6]. Pathological subtype, perineural invasion, lymphovascular invasion, depth of invasion and grade in the primary tumour are strong predictors of poor prognosis and high cancer-specific mortality. Tumour grade is a predictor of metastatic spread, and lymphatic invasion is a predictor of metastasis [7].

Thus, the aim of this study was to analyse the epidemiological and pathological characteristics and perform a statistical analysis to verify the independence between two variables related to PeCa treated at the Department of urology of Hospital Universitário Cassiano Antônio de Moraes (HUCAM), Vitória, ES, Brazil.

MATERIALS AND METHODS

This study was conducted in the State of Espirito Santo, located in the Southeast Region of Brazil, with 46,074,447 km2 in length, divided into 78 municipalities and with approximately 4 million inhabitants, of which 1,731,218 are male. The State is further divided into six mesoregions, which are:
North, Northwest, Metropolitan region and South.

This is a cross-sectional study of secondary data. The study population consisted of all records PeCa diagnosis sections in the period of January 2010 and December 2020, 79 patients with histologically confirmed PeCa were evaluated at HUCAM.

As inclusion criteria were considered medical records of men diagnosed with PeCa treated at HUCAM in the period considered; Exclusion rights were an impossibility of determination of the initial clinical/pathological staging and lack of data inherent to the study, due to the incompleteness of the medical records of patient cases.

Only one pathologist was responsible for reviewing the specimens and all patients were evaluated considering age, birthplace, ethnicity, marital status, histological type, growth pattern, site of tumor, tumor size, grade tumor, Chaux index, vascular invasion, lymphatic invasion, perineural invasion and pathologic stage (TNM staging).

We performed chi-quadrado (x^2) tests with p-value calculated by Monte Carlo simulation, with the objective of verifying the independence between two variables, for example, whether vascular invasion is related to the patient's age group. The variables used in the study were: Degree of differentiation, Pathological Staging - TNM, Chaux Index, Lymphatic Invasion, Vascular Invasion and Perineural Invasion, with the patient's race and age.

RESULTS

AGE GROUP (YEARS)	NUMBER OF CASES	%
20-30	03	3,79
31-40	04	5%
41-50	10	12.65%
51-60	20	25.31%
61-70	17	21.51%
71-80	18	22.78%
>80	07	8.86%
TOTAL	79	100%
ETHNICITY	**NUMBER OF CASES**	**%**
WHITE	19	24.05%
BROWN	45	56.96%
BLACK	13	16.45%
UNKNOWN	02	2.53%
MARITAL STATUS	**NUMBER OF CASES**	**%**
SINGLE	07	8.86%
MARRIED	51	64.55%
DIVORCED	05	6.32%
WIDOWED	08	10.12%
UNKNOWN	08	10.12%
EDUCATION LEVEL	**NUMBER OF CASES**	**%**
GRADE 1 º COMPLETE/INCOMPLETE	59	74.68%
GRADE 2º COMPLETE/INCOMPLETE	17	21.51%
SUPERIOR	01	1.26%

UNKNOWN	2	2.53%

TABLE 1- Epidemiological distribution of Penis Cancer cases that occurred in Espírito Santo from 2010 to 2020.

Source: Information from the records diagnosed at the University Hospital Cassiano Antônio Moraes - HUCAM.

Ages ranged from 25 to 87 years, with a mean of 62 years (Table 1). Of the 79 patients, 19 (24,05%) were white, 45 (56,96%) brown and 13 (16,45%) black. In this series, 51 (64,55%) patients were married, 07 (8,86%) were single, 05 (6,32%) divorced and 08 (10.12%) widowed.

Of the 79 patients, 36 (45,56%) were from the metropolitan region, 07 (8,86%) from the north, 14 (17,72%) were from the northwest and 22 (27,86%) from the south of the Espírito Santo state (Figure 1).

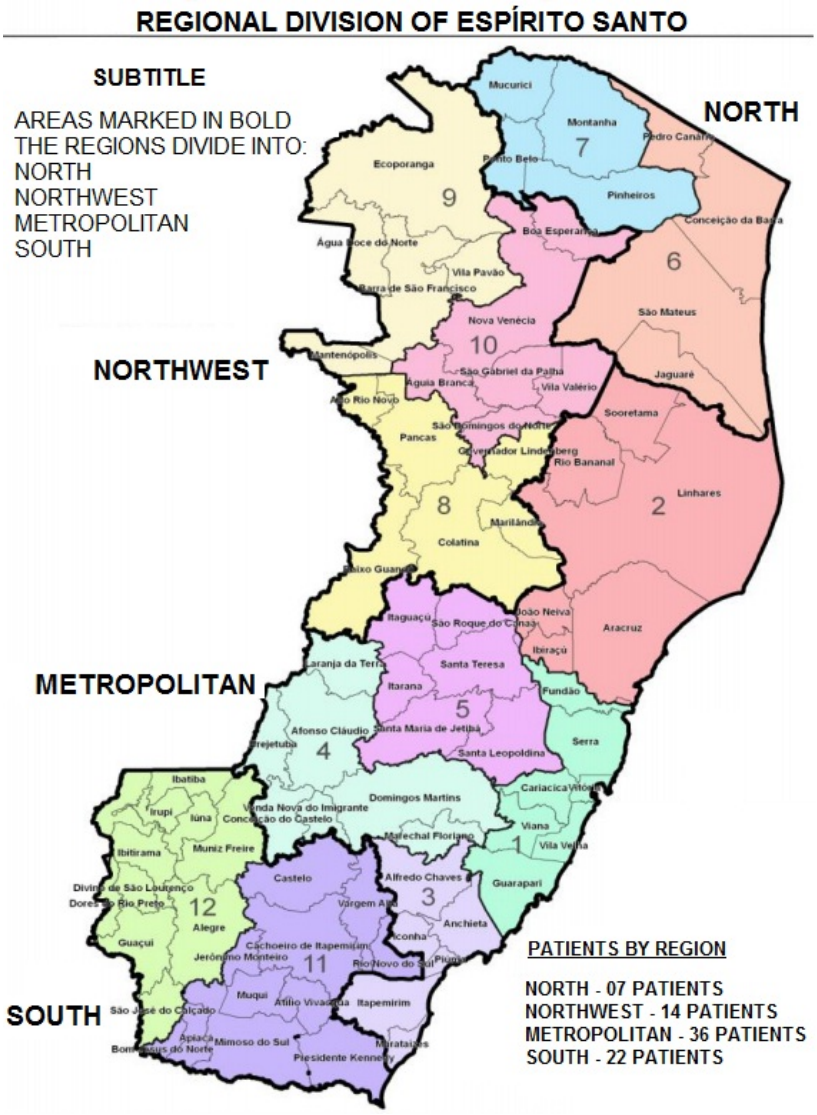

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Figure 1. Distribution of Penile Cancer cases that occurred in Espirito Santo in the period from 2015 to 2020 according to region.

Source: Information from the records diagnosed at the University Hospital Cassiano Antônio Moraes - HUCAM.

In this series only 4 (6,32%) patients had been circumcised.

In relation to pathological variables studied, 77 (97,46%) patients present squamous cell carcinoma of the penis and the lesion size ranged from 0,5 cm to 10 cm (mean 3,39 cm).

Of the 79 patients, 41 (51,89%) had lesions on the glans, 9 (11,39%%) in the foreskin, 2 (2,53%) in the body of the penis.

Based on WHO classification, 35 patients (44,30%) had grade I tumors, 34 (40,50%) grade II and only 10 (12,65%) grade III and of these patients, 2 (2,53%) had carcinoma in situ (Ca in situ), 22 (27,84%) had commitment of subepithelial connective tissue (T1), 24 (30,37%) had corpus spongiosum infiltration (T2), 20 (25,31%) had corpus cavernous infiltration (T3), no patients adjacent structures involvement (T4) and 10 (12,65%) patient only excisional biopsy was performed as definitive treatment.

Vascular invasion was observed in 12 (15,18%) patients, lymphatic invasion was observed in 7 (8,86%) patients and perineural invasion was observed in 23 (29,11%) patients of the 79 patients.

Regarding Chaux Index, 16 patients (20,25%) had Index 2, 19 (24,05%) had Index 3, 13 (16,45%) had Index 4, 19 (24,05%) had Index 5, 9 (11,39%) had Index 6, 1 (1,26%) had Index 7 and 02 (2,53%) were not evaluated.

PATHOLOGICAL VARIABLES	NUMBER OF CASES	%
CEC	77	97.46%
PIN	02	2.53%
GRADE	**NUMBER OF CASES**	**%**
G1	35	44.30%
G2	32	40.50%
G3	10	12.65%
UNKNOWN	02	2.53%
TUMOR STATUS	**NUMBER OF CASES**	**%**
PIN	02	2.53%
Ta	01	1.26%

T1	22	27.84%
T2	24	30.37%
T3	20	25.31%
T4	00	00%
EXCISIONAL BIOPSY	10	12.65%
VASCULAR INVASION	**NUMBER OF CASES**	**%**
PRESENT	12	15.18%
ABSENT	60	75.94%
UNKNOWN	07	8.86%
LYMPHATIC INVASION	**NUMBER OF CASES**	**%**
PRESENT	07	8.86%
ABSENT	65	82.27%
UNKNOWN	07	8.86%
PERINEURAL INVASION	**NUMBER OF CASES**	**%**
PRESENT	22	27.84%
ABSENT	50	63.29%
UNKNOWN	07	8.86%
CHAUX INDEX	**NUMBER OF CASES**	**%**
CHAUX 1	00	00%
CHAUX 2	16	20.25%
CHAUX 3	19	24.05%
CHAUX 4	13	16.45%
CHAUX 5	19	24.05%
CHAUX 6	09	11.39%
CHAUX 7	01	1.26%
UNKNOWN	02	2.53%
TUMOR LOCATION	**NUMBER OF CASES**	**%**
FORESKIN	09	11.39%
GLAND	41	51.89%
SHAFT PENIS	02	2.53%
ENTIRE PENIS	27	34.17%
SURGICAL TECHNIQUE	**NUMBER OF CASES**	**%**
GLANDECTOMY	29	36.70%
PARCIAL PENECTOMY	40	50.63%
RADICAL PENECTOMY	09	11.39%
UNKNOWN	02	2.53%

TABLE 2- Pathological distribution of Penile Cancer cases that occurred in Espirito Santo in the period from 2010 to 2020.

Statistical analysis was performed using the chi-square method, evaluating the relationship between vascular invasion and age of patients with penile cancer. Showing that vascular invasion has a statistically significant relationship with the patient's age group. As p-value = 0.00449 < p-value = 0.05. with no statistical significance (p>0,05) when compared to other reported statistical variables.

VASCULAR INVASION	**PRESENT**	ABSENT	Valor p
20-30 YEARS	03	00	
31-40 YEARS	00	02	
41-50 YEARS	00	05	
51-60 YEARS	03	17	0,00449
61-70 YEARS	04	13	
71-80 YEARS	02	16	
>80 YEARS	00	07	

TABLE 3 - Vascular Invasion x Age Group (Espirito Santo in the period from 2010 to 2020).

DISCUSSION

PeCa is rare in developed countries with an incidence of 0.3–0.6 per 100 000 in Europe and North America. Incidence rates diversify among different populations with less developed nations having the highest incidence. This disease represents a great impact on public health issue and accounts for up to 17% of all malignancies in some regions. Interesting, Israel reports the lowest incidence which has been related to high neonatal circumcision rates [1, 2].

The annual age-adjusted incidence is 8.3/per 100,000 in Brazil and the geographical distribution of the disease is poor known, due to the small number of publications about it. These tumors correspond to 2% of malignant neoplasms of the being five times more prevalent in the regions North and Northeast in comparison with the Central-West, South and Southeast [8]. Favorito et al. showed the prevalence of penile

cancer in the Southeast and Northeast, with rates of 45.54% and 41.07%, respectively. This very close values were attributed the large migration to the Southeast, because it is the most developed economic region in the country [9]. In our study, all patients were residents in the state of Espírito Santo.

There were 9,743 hospital admissions related to PeCa from 1992 to 2017. The expenses with admissions related to this condition in this period were US$ 3,002,705.73 (US$ 115,488.68/year). The mortality rates of PeCa in Brazil were 0.38/100,000 man, and 0.50/100,000 man in the North Region [10].

PeCa is characterized by a rise incidence with age, with a top in the sixth decade but it does occur in younger men [4]. In our series, we observed only 03 (3,79%) of patients aged between 21-30 years. The percentage increased in the fifth decade of life with 10 (12,65%) and peaked in the sixth, with an incidence of 20 patients (25,31%).

Obesity and poor personal hygiene which can be markers of poor public health have also been related with PeCa development. One study examining the association of obesity and penile cancer incidence showed a 53% risk increase for most extreme body mass index (BMI) [11]. Low socioeconomic status is generally associated with increased cancer risk [12].

Muir CS et al observed a preponderance of 2:1 in black men, although some series show no racial predisposition [13, 14]. In our series, only 13 (16,45%) were black and 19 (24,05%) were white, which differs from the observed in some studies.

Marital status also seems to be related to the risk of development PeCa with a population-based study showing decreased incidence rates in married men compared to those who are single or divorced [15]. However, in this work 51 (64,55%) were married, 20 (25,3%) were single, divorced or widover and 08 (10,12%) no information.

Circumcision is an effective treatment for recurrent balanitis, Chronic inflammatory and has also been used to manage recurrent urinary infection in child and young males. Therefore, neonatal circumcision has been considered benefical relating to hygiene, inflammatory disorders, and reduced risk of penile cancer [16]. In our study only 04 (6,32%) patients who had been circumcised.

Penile SCC usually originate from the glans, or coronal sulcus in 90% and less common on the penile shaft [3]. In our series, 41 (51,89%) had lesions on the glans, 9 (11,39%%) in the foreskin and, 2 (2,53%) in the body of the penis.

TNM clinical and pathological classification of penile cancer represents the most important prognostic factor in tumor diseases [20]. Grading should use the categories specified by the WHO for PeCa [3].

Chaux et al. proposed a prognostic index which included grade, anatomical level of infiltration and perineural invasion to predict the risk of inguinal lymph node metastases and 5-year survival [21].

There is a close association between the clinical stage of the primary penile lesion and the development of inguinal metastases. Involvement of the corpus cavernosum, the corpus spongiosum and/or urethra are considered important risk factors, predisposing the development of inguinal metastases in 61% to 75% of cases [22,23]. Lymphovascular embolization and perineural invasion is also related to poor prognosis [24].

The pathological characteristics of PeCa observed in this study are shown in table 6.

The statistical variables analyzed to verify if it has an association were Degree of differentiation, Pathological Staging - TNM, Chaux Index, Lymphatic Invasion, Vascular Invasion and Perineural Invasion, with the patient's race and age group.

The adopted significance level was equal to or less than 5%, p-value <=0.05.

In the case of the variables Pathological Staging and Chaux Index TNM and Chaux, we do not have the necessary information to perform the tests. In addition to not being able to perform the Monte Carlo simulation, as it had zero marginals.

As p-value = 0.00449 < p-value =0.05, there is evidence to reject the null hypothesis, that is, vascular invasion is related to the patient's age group.

CONCLUSION

Considering that the majority of penile cancer cases in the state of Espírito Santos are treated at the Department of urology of Hospital Universitário Cassiano Antônio de Moraes (HUCAM), as it is a reference in the treatment of such pathology, it can be concluded the penile cancer imposes a significant economic and social burden to the Brazilian population and the Public Health System.

The epidemiological profile and pathological characteristics of penile cancer (PeCa) revealed that it was a higher incidence in the metropolitan region where there is greater access to information, greater development and access to the health system or

should have, affecting mainly patients considered to be brown and married, mostly affecting the glans, without lymphatic, vascular or perineural invasion.

According to the studies carried out, the relationship between vascular invasion and age group showed statistical significance, concluding that the higher the age group, the greater the risk of vascular invasion, which could change the prognosis, characterizing according to the TNM stage - T1b (lymphofascular invasion).

CONFLICT OF INTEREST

None declared.

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