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Is body mass index a risk factor for lymphnode metastasis in penile cancer?

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Abstract

Introduction Obese patients with penile cancer may have more advanced disease. This study evaluated the association of obesity with penile cancer and the risk of lymph node metastases in patients who underwent inguinal lymphadenectomy.

Methods We retrospectively reviewed the charts of 197 penile cancer (PC) patients from January 2000 to December 2011. Seventy underwent inguinal lymphadenectomy. For this subgroup, chi-square analysis evaluated the correlations of sociodemographic, clinical, and pathological variables with the presence of positive inguinal lymph nodes. Patients were divided into normal weight, overweight, and obese categories according to body mass index (BMI). The mean numbers of positive and resected lymph nodes were compared for each BMI category.

Results The percentage of overweight men in the Brazilian population and among patients with PC was 52.6% and 42.8%, respectively. For patients who underwent lymphadenectomy, the mean BMIs were 25.9 ± 6. Most patients were white, married, had a lower education level, and had no history of smoking. Partial penectomy was the most frequently performed surgery; lymphovascular invasion occurred in 45.7%, and lymph node metastasis occurred in 52.9% of cases. The mean numbers of resected and positive lymph nodes for normal weight, overweight, and obesity were 21.1 and 2.2, 23.3 and 2.2, and 16.8 and 1.5, respectively.

Conclusion Overweight and obesity were less frequently seen in patients with PC than in the Brazilian population. BMI was not a risk factor for developing lymph node metastasis; the only predictive factor for lymph node metastasis was the presence of lymphovascular invasion.

Keywords Obesity, Penile cancer, Prognostic factors, Lymphadenectomy

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Introduction

Penile cancer (PC) is a rare disease. Squamous cell carcinoma (SCC) is observed in over 95% of cases [1]. The etiology is multifactorial, and 80% of cases can be cured with a multidisciplinary approach [2]. Lymph node involvement is a major prognostic factor associated with survival [2, 3]. The risk of lymph node involvement is mainly based on histopathological criteria, and there are no reliable clinical criteria for predicting lymph node disease [3–6]. Obesity is considered a risk factor for various cancers and influences the prognosis of these patients [7, 8]. Obese individuals with prostate cancer have higher rates of biochemical relapse and have more aggressive disease compared to non-obese individuals [9, 10]. A higher incidence of kidney cancer has also been demonstrated in obese patients [11]. However, to date, no study has linked obesity to the presence of lymph node involvement in patients with PC.

Barnes KT et al. analyzed patients with PC in the United States. The authors found a correlation between locally advanced disease and higher BMI. Although in this series the patients had a higher BMI when compared to the general population, this fact can be interpreted in two different ways. There is a possibility that the presence of obesity and the inflammation caused by it are a risk factor for PC. On the other hand, obesity, and penile cancer might share self-care negligence [12].

In developing countries, where PC is more prevalent, the prevalence rates of overweight and obesity among such patients have not been described. It is also unknown whether there is a relationship between BMI and disease progression or whether obesity is a limiting factor for inguinal lymphadenectomy.

The current study evaluates the relationship between body mass index (BMI) and the number and positivity of resected inguinal lymphnodes in PC patients.

Sample and methods

After local ethics committee approval (number 14096/2010) and informed consent obtained from all the participants, the medical records of 197 patients with PC treated at the Barretos Cancer Hospital (2000–2011) were retrospectively reviewed after local ethics committee approval (number 14096/2010). The Brazilian population's BMI was obtained from the most recent census carried out by the Ministry of Health and used for comparison. BMI was defined according to the WHO categorization. Pathologic staging was performed according to the TNM classification of 2002. The histological grade of the lesion was based on the "Broders" classification.

Classic radical inguinal lymphadenectomy preserving the fascia lata was performed [13], with indications including pathologic stage of the primary lesion ≥ 2 (pT ≥ 2) or pathologic stage 1 (pT = 1) with palpable inguinal lymph nodes that do not resolve after systemic antibiotic therapy for 4 weeks and patients who developed palpable inguinal lymph nodes during follow-up, the standard practice in 2000–2011.

Sociodemographic, clinical, and pathological parameters were evaluated with a focus on BMI and the number of resected lymph nodes. To comparatively study two independent variables, the pathologic staging of lymph nodes (pN) was regrouped into two dichotomous groups, (N0) vs. (N1/N2/N3). The tests evaluated the relationship of the variables with the presence or absence of positive lymph nodes using BMI as the variable of interest. Conditional logistic regression was used to examine the association between BMI and odds of positive lymph node.

Relationships between variables were assessed using the chi-square test. Odds ratios and their 95% confidence intervals were acquired by multiple logistic regression. A significance level of $p < 0.05$ was used throughout the study. The variance of the mean for the number of positive and resected lymph nodes was obtained according to the mean for each BMI category. Lymph node density was calculated by dividing the number of cancer-positive lymph nodes by the total number of harvested lymph nodes.

The weight/height records were obtained for patients' physical examination, and the BMI category of < 18.5 kg/m^2 (underweight) was included in the normal weight category due to the small number of cases.

Results

Table 1 shows the BMI results at diagnosis for the 182 patients with complete weight and height data. The mean BMI was 25.4 (kg/m^2),54.5% of patients were considered eutrophic (BMI between 18.5 and 24.9), and 2.7% were underweight and possibly malnourished (BMI < 18.5).

The percentage of PC patients with overweight or obesity was 42.8% (78 cases), whereas the estimated percentage of overweight and obesity for the Brazilian population is53% [14]. Data analysis corrected for the number of men in each group revealed that the prevalence of overweight and obesity was lower in patients with PC ($p = 0.04$).

Table 1 Weight distribution among patients with penile cancer($n = 182$)

BMI (kg/m^2)	Frequency (*N**)	Percent (%)
< 18.5	5	2.7%
18.5–24.9	99	54.5%
25-29.9 (overweigh)	51	28.0%
≥ 30 (obese)	27	14.8%
Total	182	100%

*Excluded = 15 cases

Table 2 Patients undergoing inguinal lymphadenectomy according to sociodemographic, clinical, and pathological variables ($n=70$)

Variables	Categories	*n* (%)
Age (years)	≤ 40	12 (17.1)
	41–60	34 (48.6)
	≥ 61	22 (31.4)
	Not informed	2 (2.9)
Race	White	46 (65.7)
	Non-white	23 (32.9)
	Not Informed	1 (1.4)
Education level	Illiterate	14 (20.0)
	Incomplete Primary Education	49 (70.0)
	Complete Primary Education	5 (7.1)
	Not Informed	2 (2.9)
Marriage Status	Married/Stable Union	44 (62.9)
	Single/Separated/Divorced/Widower	22 (31.4)
	Not Informed	4 (5.7)
Smoker	No	33 (47.1)
	Yes	31 (44.3)
	Not Informed	6 (8.6)
BMI	Underweight (< 18.5)	1 (1.4)
	Normal Weight (18.5–24.9)	38 (54.4)
	Overweight (25–29.9)	12 (17.1)
	Obese (≥ 30)	12 (17.1)
	Not Informed	7 (10.0)
pT Staging	T1	17 (24.3)
	T2	28 (40.0)
	T3	19 (27.1)
	T4	2 (2.9)
	Not Informed	4 (5.7)
pN Staging	N0	33 (47.1)
	N1	9 (12.9)
	N2	13 (18.6)
	N3	15 (21.4)
Histological Grade	I	16 (22.9)
	II	43 (61.4)
	III	6 (8.6)
	Not Informed	5 (7.1)
Lymphovascular Invasion	Yes	32 (45.7)
	No	22 (31.4)
	Not Informed	16 (22.9)

Table 2 shows the results for the variables among the 70 patients who underwent ILND. The mean age was 54.78 ± 14.6 years (range 24–88 years). The mean BMI was 25.9 ± 6.0. ILND was performed bilaterally in 61 patients (87.1%) and unilaterally in 9 patients (12.9%).

Table 3 shows the analysis of the means for the numbers of resected and positive lymph nodes and lymph node densities according to BMI categories for 63 patients. The mean number of resected lymph nodes per patient was 21 ± 2.15: 11.49 ± 6 on the right and 11.08 ± 5.8 on the left. There were no significant differences between BMI categories regarding the average number of resected lymph nodes, positive lymph nodes, and lymph node density.

Table 4 shows the univariate analysis of patients undergoing ILND. There was an association between the presence of lymph node metastasis and lymphovascular invasion. BMI was not a risk factor for lymph node metastasis In the multivariate model, the only independent risk factor for lymph node metastasis was the presence of lymphovascular invasion.

Discussion

The association between obesity and PC is underexplored in the literature. This is the first study focusing on obesity and penile cancer lymphadenectomy. While limited by its retrospective design, it could not find any robust association between BMI and LN involvement.

The worldwide prevalence of obesity more than doubled between 1980 and 2008. According to the most recent census (Vigitel-2011) by the Ministry of Health, nearly half of the population is above the ideal weight for their height. Among men older than 18 years, 52.6% were overweight or obese, and 15.6% were obese [14, 15]. BMI was used to define overweight/obese in our cohort and national figures.

The increase in body weight is a risk factor for several cancers, such as colon, breast, endometrium, kidney, prostate, and others [16]. In addition, obese individuals with cancer have greater cancer-specific mortality than non-obese individuals [17].

The possible biological mechanisms attributed to the "obesity-cancer" link are still poorly understood. Some

Table 3 Mean (± SD) numbers of resected lymph nodes, positive lymph nodes, and lymph node density according to BMI ($n=63$)

BMI (kg/m^2)	$N=63$ *	Resected Lymph Nodes		Positive Lymph Nodes		Lymph node density # (Mean)
		Mean (Range)	SD	Mean	SD	
< 25	39	21.1 (2–54)	11.7	2.2	4.0	0.16
25-29.9 (overweigh)	12	23.3 (7–49)	13.9	2.2	3.1	0.11
≥ 30 (obese)	12	16.8 (4–26)	6.0	1.5	1.8	0.10
p		$p=0.35$		$p=0.84$		$p=0.68$

*7 cases were excluded (missing data on medical records)

p = Analysis of variance between means

SD = Standard deviation

Lymph node density was calculated by dividing the number of cancer positive lymph nodes by the total number of harvested lymph nodes

Table 4 Patients' numbers and percentages according to the pN staging and sociodemographic, clinical, and pathological variables*

Variables	Categories	pN Staging		*p*-value#
		N0	N1-3	
		n (%)	*n* (%)	
Age (years)	< 55	13 (37.1)	22 (62.9)	0.090
	≥ 55	19 (57.6)	14 (42.4)	
Race	White	17 (37.0)	29 (63.0)	0.260
	Non-white	15 (65.2)	8 (34.8)	
Education level	Illiterate	9 (64.3)	5 (35.7)	0.467
	Incomplete Primary Education	22 (44.9)	27 (55.1)	
	Complete Primary Education	2 (40.0)	3 (60.0)	
Marriage Status	Married/Stable Union	19 (43.2)	25 (56.8)	0.600
	Single/Separated/Divorced/Widower	11 (50.0)	11 (50.0)	
Smoker	No	16 (48.5)	17 (51.5)	0.808
	Yes	14 (45.2)	17 (54.8)	
BMI (kg/m^2)	< 25	20 (51.3)	19 (48.7)	0.544
	25-29.9 (overweight)	4 (33.3)	8 (66.7)	
	≥ 30 (obese)	6 (50.0)	6 (50.0)	
pT Staging	T1	8 (47.1)	9 (52.9)	0.402
	T2	12 (42.9)	16 (57.1)	
	T3/4	13 (61.9)	8 (38.1)	
Histological Grade	I	8 (50.0)	8 (50.0)	0.856
	II	21 (48.8)	22 (51.2)	
	III	2 (33.3)	4 (66.7)	
Lymphovascular Invasion	No	20 (90.9)	2 (9.1)	< 0.001
	Yes	3 (9.4)	29 (90.6)	

* Numbers vary due to missing data

Univariate analysis

hypotheses have identified phenomena arising from obesity, such as hormonal changes and inflammation mediated by cytokines and cellular growth factors (e.g., insulin-like growth factor 1 [IGF-1]), as responsible for the genesis of cancer [11, 16].

In 101 patients diagnosed with PC between 1974 and 2011 in one region of a developed country, the mean BMI was 31.8 kg/m^2, which was greater than the mean for the general population without PC. Furthermore, multivariate analysis revealed a direct correlation between advanced disease and having a higher BMI at the time of diagnosis. The high incidence of PC in obese individuals could be related to neglected self-care shared by both conditions. Also, obesity is associated with the embedded penis and greater smegma accumulation. Likewise, local physical examinations would be hampered, thereby delaying disease diagnosis [12].

The current study was retrospective and had clear limitations, such as difficulty in collecting data, missing data, and non-standardized therapeutic approaches. In this study, the mean BMI was 25.4 kg/m^2, and the prevalence of overweight and obesity among PC patients was less than that of the control population ($p = 0.04$). Most patients with PC had a BMI < 24.9 (57.2%).

The epidemiological profile of PC in Brazil involves individuals living in rural areas, smokers, and individuals with lower educational level and low income [18–20]. Low levels of schooling correlate with lower rates of overweight and obesity among men in these areas. This fact may explain the lower prevalence of overweight and obesity in men with PC in this study. Individuals living in developed areas may be exposed to different risk factors concerning PC when compared to developing region patients, who show high HPV co-infection rates predominating high-risk subtypes [21, 22].

The most important factor for PC onset in populations from poor areas is the lack of information on prevention and limited access to health services. Some of these patients inhabit rural areas, where they begin sexual activity as early as adolescence and are subject to factors such as smoking, bestiality, and poor genital hygiene, which would contribute to PC development at younger ages [23].

Of the 70 patients who underwent ILND, 35 were younger than 55 years. Of the three categories established for BMI (normal weight, overweight, and obese), none was a risk factor for lymph node involvement ($p = 0.54$). No specific studies in the literature relate BMI to lymph node staging and the number of resected lymph nodes in patients with PC. For PC, this fact leads us to believe that both local irritating factors and primary tumor characteristics, such as histological type, degree of differentiation,

and lymphovascular invasion, are more relevant in the genesis and metastasis of PC than simply gaining weight.

In the present study, the mean number of resected lymph nodes was 21 ± 2.15 for each patient. In a study published in 2010, the authors obtained a similar mean number of resected lymph nodes using a similar technique respecting the classic anatomical dissection boundaries, confirming our study as representative and reproducible [13].

There were no significant differences between the normal weight, overweight, and obese patient groups in the mean number of positive lymph nodes ($p = 0.35$), the number of resected lymph nodes ($p = 0.84$), and lymph node density ($p = 0.68$). Despite the tendency to resect fewer lymph nodes (16.8 versus 22.2) with a lower mean number of positive lymph nodes (1.5 versus 2.2) in obese patients compared to normal-weight and overweight individuals. A study published in 2003 showed that for rectal tumors, obesity limits the number of resected lymph nodes [24]. In 2003, another study reported that obesity limited the identification of sentinel lymph nodes in patients with breast cancer [25]. For PC, the present study is the first to correlate BMI with the presence or absence of positive nodes in lymphadenectomy.

The pathologic stage (pT) ($p = 0.402$) and the degree of cell differentiation ($p = 0.856$) were not predictors of lymph node metastasis. This finding indicates that local staging may be flawed when used to predict prognosis [26]. Some studies stress the importance of the degree of cell differentiation in the evaluation of lymph node metastases [27, 28]. However, similar to the present study, other studies found no relationship between the degree of differentiation and the risk of lymph node metastasis [6]. The only variable that was significantly associated with the risk of lymph node involvement was the presence of lymphatic embolization ($p < 0.001$).

It is important to emphasize that the BMI has not influenced the technique, surgical approach, or completeness of lymphadenectomy and recognize the current study's limitations, mainly related to its retrospective design, susceptible to missing and incomplete data. Future prospective studies are encouraged to limit confounding factors in interpreting the relationship between BMI and lymph node metastasis and lymphovascular invasion, as the key predictor of disease progression, warrants further research to explore its biological mechanisms, mainly in obesity. Also, future studies should explore the potential differences between early- and late-onset obesity.

Conclusions

The occurrence of overweight and obesity had no greater risk of presenting with positive lymph nodes or having fewer resected lymph nodes compared to normal-weight patients. Obesity was not a limiting factor for lymphadenectomy in patients with penile cancer. While the proportion of PC patients who were overweight and obese was lower than the prevalence of these disorders in the general Brazilian population, the current study was underpowered for such a comparison.

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Author contributions
RDM: data curator and prepared the manuscript. EF, AARJ, FS, RNF: collected clinical data, processed samples. PS, SFS: co-supervision and intellectual contribution. LOR, RBR– study design, supervision, and funding acquisition. All the authors approved the final submitted version.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
The authors certify that the study was performed under the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Barretos Cancer Hospital ethics committee approval (number 14096/2010). All the participants signed informed consent forms before participating.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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