Profile of Patients with Penile Neoplasms who Have Undergone Penectomy

ORIGINAL

Maria das Neves Figueiroa[1,2], Maria Lúcia Neto de Menezes[2], Leonardo Nogueira Tavares[2], André Frederico Franklin Maciel[3], Laurecir Gomes[1]

1 Department of Functional and Structural Biology, São Paulo State University of Campinas (UNICAMP). Campinas, SP, Brazil.
2 School of Nursing "Nossa Senhora das Graças" of the University of Pernambuco (FENSG/UPE). Recife, PE, Brazil.
3 Department of Urology, Pernambuco State Cancer Hospital (HCP). Recife, PE, Brazil.

Contact information:

Neves Figueiroa.

Address: Rua Doutor Malaquias, nº 145, ap. 1403. Graças, Recife, PE, Brazil, CEP:52050-060.
Tel: 81-99979-6145

✉ nevesfigueiroa@hotmail.com

Abstract

Introduction: Penile cancer accounts for 10% to 20% of the male urogenital tumors. In Brazil, the North and Northeast regions have the highest rates.

Objective: Analytical, retrospective, and cross-sectional study addressing the profile of individuals with penile neoplasms who have undergone penectomy in Recife, Pernambuco, Brazil.

Methods: The population of this study consisted of 305 men who underwent penectomy at the Pernambuco State Cancer Hospital (HCP), from 2000 to 2009. There was prevalence of elderly, low-schooling and low-income men, as well as individuals from municipalities outside the Metropolitan Region of Recife.

Results: Poor hygiene, smoking, and phimosis were the main risk factors identified. Patients showed epidermoid carcinoma (type I) and metastasis. The early signs and symptoms were tumor and painful ulcer.

Conclusion: Most of the individuals have undergone partial penectomy.

Introduction

Cancer is a broad term, used to describe a group of more than 200 types of diseases that affect specific tissues or bodily organs. It is characterized as a major public health problem, causing more than 6 million deaths a year; it represents about 12% of the causes of death

International Archives of Medicine
Section: Epidemiology
ISSN: 1755-7682

2017

Vol. 10 No. 223
doi: 10.3823/2493

in the world [1]. Pathology begins when the genetic material of a cell is damaged in some way, causing the cell to divide at an uncontrolled rate. The resulting cell group often forms a nodule, commonly called tumor [2].

According to the World Health Organization (WHO), the distribution of cancer deaths is not homogeneous around the world. Data show a 15% to 25% increase in the mortality rate in developed countries. The rates are lower in developing countries, however they reach from 6% to 9%, with expectation to increase from 5.4 million in 2000 to 9.3 million in 2020, according to population projections [3, 4].

Penile cancer is a relatively rare disease, whose incidence rate varies according to the region. Penile neoplasm is rare in North America and Europe, but its incidence is high and worrisome in Latin America, Africa, and Asia. In the United States of America (USA), the age-standardized incidence rate ranges from 0.3 to 1.8 per 100,000, and in Israel it is 0.1 per 100,000, differing, for instance, from some Brazilian areas, with rates between 1.5 and 3.7 per 100,000 [5, 6]; especially in the North and Northeast regions, it even surpasses the cases of prostate and bladder cancer [7, 8].

In the case of Brazil, this disease represents 2% of the neoplasms affecting men and it is about 5 times more common in the North and Northeast regions, when compared to the South and Southeast regions. In regions of higher prevalence, penile tumors even outnumber prostate and bladder neoplasms [9, 10]. Studies indicate that the highest rates in the world are observed in Recife, Pernambuco, and Fortaleza, Ceará, Brazil [11].

The penile cancer morbidity rate concerns the stage at which it begins to be treated. Thus, one of the great challenges for pathology prevention and control refers to delay in seeking medical care, which is often associated with the social stigma of male illness, particularly when the lesions occur in the genital region, but also due to the strong sociocultural connotation of compromised masculinity that leads to denial of disease [12].

Comparative studies between men and women have proven the fact that men are more vulnerable to diseases, above all severe and chronic diseases, and they die earlier than women [13]. Among the aspects that explain this phenomenon, it is worth highlighting the fact that men do not seek, as women do, primary health care (PHC); men seek ambulatory care and medium- and high-complexity hospital care. Faced with such evidence, the Ministry of Health designed the Brazilian National Policy for Comprehensive Men's Health, which aims at qualification from the perspective of developing the mechanisms to strengthen the PHC, guaranteeing, above all, health promotion and prevention of health problems [13].

Epidemiological analysis of the penile cancer cases indicates that, in relation to the socio-economic-cultural profile of patients with this disease, the neoplasm affects mainly men from a disadvantaged social class and those with a low schooling level, and its areas of highest incidence are located in the poorest regions of developing countries [9, 10].

Penile neoplasm can cause loss of function, disfigurement, and death. About 50% of patients with this pathology survive, on average, for five years, but the prognosis varies depending on the state of lymph node involvement and the existence of metastasis [11].

Most tumors derive from the surface of the mucosa extending from the foreskin to the urethral meatus [10]. Penile tumors tend to evolve slowly, first superficially, invading the chorion, the spongy gland tissue, and the corpora cavernosa. Infiltration of the urethra is rare and it usually occurs only in advanced stages of tumors of the corpora cavernosa. The biological behavior of these tumors tends to be uniform, with dissemination to inguinal lymph nodes, pelvic and periaortic lymph nodes, and they rarely show visceral involvement [14-16].

The most common sites of lesion are penile glans, foreskin, and coronal sulcus. Symptoms generally include bleeding and smelly genitalia. Patients can also notice masses in the inguinal region, which may be a consequence of local inflammation and infection or evidence of metastasis to lymph nodes. Patients with advanced disease may complain of fatigue, weight loss, and bone pain. Lesions vary in size and the clinical presentation of tumor depends on histological differences observed in the organ. Metastatic lesions involving the corpora cavernosa are often caused by multiple and palpable nodules [10].

The most common histological types of penile cancer include carcinoma of squamous origin and carcinoma in situ. The latter is known as Queyrat's erythroplasia and Bowen's disease, which occurs in the form of non-invasive epithelial cell changes [12].

Penile tumors, according to their histopathological characteristics and forms of presentation, are classified as: epidermoid carcinoma (most common), basaloid carcinoma, verrucous carcinoma, sarcomatous carcinoma, verrucous epidermoid carcinoma, and papillary carcinoma [17, 18].

Analyzing the histological levels of cancer may be correlated with tumor depth, as well as the risk of inguinal metastasis. The most commonly used histological type of penile cancer is Broders'. This classification is fundamentally based on type of keratinization, number of mitoses, and nuclear pleomorphism [11, 19, 20].

Risky sexual behavior, such as a large number of sexual partners, also constitutes risk for penile neoplasm. Traumas favor inflammation of the glans (balanitis), offering a risk from 3% to 9% for developing this neoplasm. Human immunodeficiency virus (HIV) infection is associated with an 8-fold increased risk of penile cancer, but this may be associated with a higher incidence of human papillomavirus (HPV) in men with HIV [5, 12, 21].

Monitoring and treatment of men with squamous cell carcinoma of the penis depends on correct diagnosis and classification and malignant tumor staging. Men with cutaneous lesions in the penis, especially those with risk factors, should be the target of great suspicion of penile carcinoma. For the correct diagnosis, it is needed to conduct a careful anamnesis, including the time elapsed between the emergence of lesion and the present moment, as well as the evolution of lesion and previous treatments. It is appropriate to undertake a comprehensive review of systems to identify signs and symptoms of regional dissemination and advanced disease [20].

In clinical examination of the primary penile lesion, we must evaluate and register the number of lesions, the tumor sizes, the sites involved, such as foreskin and/or glans, the limits of morphology, the lesion features (flat, papillary, nodular, ulcerative), and the relationship with other structures, such as spongy body, corpora cavernosa, and urethra [12, 17].

The only means to confirm the diagnosis of primary tumor is biopsy in the central portion of the lesion and in depth [17]. In the presence of phimosis, a dorsal incision of the foreskin is needed for better lesion exposure. Magnetic resonance imaging may be used, exceptionally, for evaluating tumors whose local extent could not be adequately determined by physical examination. Ultrasonography may also be used for this purpose, but it has lower sensitivity than magnetic resonance imaging.

The ideal method of evaluating regional lymph nodes in patients with epidermoid carcinoma is still controversial. About 50% of the palpable lymph nodes do not have neoplastic involvement and, on the other hand, about 20% of the patients without detectable lymph node involvement on palpation have metastasis. Ultrasonography-driven fine needle aspiration biopsy may be employed to better assess micrometastasis, in patients without palpable lymph nodes, but it shows low sensitivity (39%), despite the 100% specificity [18].

Due to low sensitivity of the methods employed, the only reliable process of regional lymph node

INTERNATIONAL ARCHIVES OF MEDICINE
SECTION: EPIDEMIOLOGY
ISSN: 1755-7682

2017

Vol. 10 No. 223
doi: 10.3823/2493

evaluation is regional lymphadenectomy, which can, in addition to establish staging, cure minimal lesions. For distant metastasis evaluation, we may resort to chest radiography and computed tomography of the abdomen and pelvis. Positron emission tomography (PET), either coupled to computed tomography (PET-CT) or not, is a promising method [17, 22, 23].

Distant metastasis events are uncommon. In patients who died from disseminated penile cancer, the following distant metastasis sites were identified: lymph nodes, liver, lungs, heart, kidneys, adrenal glands, bones, skin, thyroid, brain, pancreas, spleen, and pleura. Large lesions and those with unfavorable histology are more likely to spread [20].

The penile cancer treatment may rely on surgery, radiotherapy, and chemotherapy, and it depends on the tumor extent. In a large number of cases, surgery is the best procedure for local control of pathology. Early diagnosis may prevent organ amputation, which produces physical, sexual, and psychological sequelae [2].

Untreated or ineffectively treated patients usually die from complications secondary to inguinal metastasis, i.e. bleeding from large vessel tumor lesions or septic processes. For these reasons, penile cancer poses challenges for reducing its incidence [10, 12].

It is hard to devise guidelines on prevention of malignant penile diseases, since variation in the incidence of this cancer may hinder adherence to standard strategies, such as HPV vaccination or foreskin excision in early childhood. On the other hand, the fight against smoking must be strongly advised through public health programs [24].

For these reasons, scholars stress the importance of conducting research that provide better options for treatment and management of premalignant lesions and favor prevention and improve case prognosis. Regarding the determination of case prognosis, it is known to depend on clinical factors, anatomopathological disease staging, and presence of biomarkers [17, 25].

This study addresses the profile of patients with penile cancer in the Northeast region of Brazil, especially in Pernambuco.

Methods

This is an analytical, retrospective, cross-sectional study, carried out in Recife, capital of Pernambuco, a city located in the Brazilian northeastern coast, 800 km away from other two metropolis, Salvador and Fortaleza, constituting along with them a strategic space of regional references.

The population of this study consisted of all individuals diagnosed with penile cancer who underwent penectomy between 2000 and 2009 at the state referral center, the Pernambuco State Cancer Hospital (HCP). Data collection was conducted by means of a survey with 305 medical records of the individuals who fit the criterion indicated above.

All variables analyzed are related to the sociodemographic indicators, exposure to risk factors such as: smoking, hygiene habits, history of risk for penile cancer, data related to diagnosis, histological level, staging, and treatment adopted.

The study was carried out according to the Declaration of Helsinki and Resolution 196/1996, from the Brazilian National Health Council (CNS), referring to the ethical aspects of research involving human beings, after approval by the Research Ethics Committee of the HCP, under Protocol 0018.0.447.000-11.

Results

We analyzed 305 cases of patients at the HCP who underwent total or partial penectomy between 2000 and 2009.

Surveying the profile of patients **(Table 1)** who were included in this study allowed us to find that most of them were individuals ≥ 60 years (54.8%), with little or no schooling (35.8%), rising to 95.5% when excluding unreported figures. Their occupa-

INTERNATIONAL ARCHIVES OF MEDICINE
SECTION: EPIDEMIOLOGY
ISSN: 1755-7682

2017

Vol. 10 No. 223
doi: 10.3823/2493

tion is related to rural labor (28.5%) or the individuals are retired (14.1%), their family income is up to 5 minimum wages (48.2%), rising to 87.8% when excluding unreported figures. Patients lived or came from municipalities outside the Metropolitan Region of Recife (68.9%).

The risk factors **(Table 2)** that showed prevalence in more than 50% of the cases of penile cancer involved in this study were body hygiene

Table 1. Sociodemographic characteristics of penectomized patients. Recife, 2000-2009.

Characteristics	N	%
Age group		
≤ 40 years	31	10.2
41 to 59 years	105	34.4
≥ 60 years	165	54.1
Uninformed	4	1.3
Schooling		
No schooling	56	18.4
Incomplete Elementary School	41	13.4
Complete Elementary School	9	3.0
High School or Higher Education	5	1.6
Uninformed	194	63.6
Occupation		
Farmer	87	28.5
Retired	43	14.1
Others	65	21.3
Uninformed	110	36.1
Family income		
No income	9	3.0
Up to 5 minimum wages	138	45.2
> 5 minimum wages	1	0.3
Uninformed	157	51.5
Origin		
Recife	38	12.4
Municipalities within the MRR	39	12.8
Municipalities in Pernambuco – outside the MRR	210	68.9
Municipalities in other states	10	3.3
Uninformed	8	2.6

Source: Prepared by the authors. MRR: Metropolitan Region of Recife.

Table 2. Exposure to risk factors and clinical conditions of penectomized patients. Recife, 2000-2009.

Characteristics	N	%
Exposure to risk factors		
History of phimosis	197	64.6
Smoking	163	53.4
Poor hygiene	271	88.8
Early signs and symptoms		
Tumor	274	89.8
Local pain	146	47.8
Ulcer/wound	134	43.9

Source: Prepared by the authors.

(88.8%), presence of phimosis (64.6%), and smoking (53.4%).

Analyzing the association between age and exposure to risk factors for penile cancer, we identified that poor hygiene and phimosis were the most prevalent risk factors at all ages. However, when considering smoking, the highest prevalence of this indicator was among individuals ≤ 60 years. Among the risk factors, however, there were also a lower prevalence of sexual risk behavior and use of alcohol and illicit drugs. The latter were observed in age groups < 60 years.

Evidence of cancer **(Table 2)** has emerged from a primary penile tumor (89.8%), accompanied by local pain, cited by 47.8% of the patients as the early symptom and showing ulcers or wounds in 43.9% of the reports of signs noticed on an early basis by patients.

According to **Table 3**, squamous histological carcinoma is the most common, observed in 90.9% of the penectomized patients. In relation to staging, type I occurred in 61% of the subjects, with metastasis in 32.2%, and there was macroscopic report in 93.1% of the individuals.

When data on pathologic staging, age group, and distribution of cases of positive metastasis were associated, type II staging was more frequent in in-

Table 3. Characteristics related to the diagnosis and staging of penectomized patients. Recife, 2000-2009.

Characteristics	N	%
Diagnosis		
Squamous histological cancer	273	89.6
Verrucous carcinoma	5	1.6
Squamous + verrucous carcinoma	4	1.3
Other	5	1.6
Uninformed	18	5.9
Staging		
Type I	186	61.0
Type II	57	18.7
Type III	14	4.6
Type IV	4	1.3
Uninformed	44	14.4
Metastasis		
Yes	92	30.2
No	156	51.1
Uninformed	57	18.7
Macroscopic report		
Yes	284	93.1
No	4	1.3
Uninformed	17	5.6

Source: Prepared by the authors.

Table 4. Characteristics related to the treatment of penectomized patients. Recife, 2000-2009.

Characteristics	N	%
Proposed intervention		
Total penectomy	101	33.0
Partial penectomy	204	67.0
Clinical treatment		
Radiotherapy	32	10.5
Chemotherapy	38	12.5
Radiation therapy + chemotherapy	17	5.6
Other	4	1.3

Source: Prepared by the authors.

dividuals from more advanced age groups, reaching up to 50% of the cases among men $\geq$ 60 years.

Resorting to the distribution of cases where metastasis occurred, in relation to the age group, we evidenced a higher prevalence of metastasis among individuals > 60 years.

Regarding surgical intervention **(Table 4)**, partial penectomy was the most prevalent type of treatment, it was performed in 67% of the individuals analyzed, out of these, the majority were $\leq$ 60 years (68.8%) and type I (81.2%). Chemotherapy was adopted in 12.5% of the treatments (reaching 41.8% when uninformed data are disregarded).

The survey of patients' origin and the type of staging showed that, among those with type II, the majority (75%) came from other municipalities within the Metropolitan Region of Recife and the state of Pernambuco, but not from the capital city, Recife.

Discussion

Epidemiological analysis of the penile cancer cases corroborates the national and international literature on the theme, since most cases affect men $\geq$ 60 years [26-28]. About 60% of the cases occur in men $\geq$ 65 years, however, young individuals may also be affected, as about 22% of the cases are registered in patients $\leq$ 40 years and 7% in patients $\leq$ 30 years of age. Comparing data of the world population to those of Brazil, penile cancer occurs earlier in Brazil, since the fourth decade of life [9]. Considering the social class and schooling level, these are generally low, and the areas of highest incidence are located in the poorer regions of developing countries [9, 10].

As for the risk factors, a high prevalence of cases of men with poor hygiene, phimosis, and those reporting smoking throughout life was identified. These factors have also been identified in other studies [27-30], among which people cited as main risk factors the presence of phimosis, low socioeconomic

INTERNATIONAL ARCHIVES OF MEDICINE
SECTION: EPIDEMIOLOGY
ISSN: 1755-7682

2017

Vol. 10 No. 223
doi: 10.3823/2493

conditions, large number of sexual partners, history of sexually transmitted disease, especially HPV, poor hygiene, smoking, inflammation, and presence of sores or ulcerations in the penis.

The prevalence of phimosis among patients with this type of cancer has already been described [24, 31], it is 74%, and on the other hand it has been found that, in countries where neonatal circumcision is practiced, such as Israel and the USA, the occurrence of penile cancer was extremely low, with rates < 1%. Phimosis can determine the retention of smegma [27], favoring the conditions of chronic irritation with or without bacterial inflammation of the foreskin and glans, which may represent a critical component in tumor development and progression. Our data corroborate the literature, with presence of phimosis in 64% of the patients analyzed. Phimosis has also been described as strongly associated with the risk of penile cancer because it hampers hygiene of the glans, inner foreskin layer, and coronal sulcus, which are areas of high incidence of HPV lesions. For this reason, circumcision, defined as the foreskin excision, is a significant protective factor against this neoplasm, in addition to urinary tract infections and sexually transmitted diseases, thus it is regarded as a measure with a major impact on public health [32, 33]. In association with the presence of phimosis, we observed that the incidence of lack of hygiene among the patients analyzed was 88.8%, indicating poor body care. These two factors combined show the penile vulnerability to installation of pathological agents that lead to cancer development.

When analyzing the set of signs and symptoms that accompanied the occurrence of penile cancer, out of the 305 study subjects, 89.8% had the lesion as the early sign of the disease. The occurrence of pain, a symptom registered in most of the documents analyzed, is due to association with inflammatory processes, such as balanitis or lichen. The lesion usually appears as a fixed mass or nodule in 47% of the cases, a wound or ulcer in 35%, and/or inflammatory lesion in 17% [12]. The lesion may be hidden by the foreskin [12], particularly in patients with phimosis, a marked risk factor among the subjects studied. The presence of lesions in the penis may also be associated with pain, discharge, bleeding, and odor. In turn, patients with advanced cancer may complain of fatigue, weight loss, and bone pain [34-37].

The result of the 305 cases surveyed in this study showed that 89.6% of the patients had squamous tumor, corroborating the literature. This is the most common histological type, accounting for 95% of the cases of penile neoplasms [38, 39]. The remaining lesions result from metastasis stemming from tumors in other organs, sarcomas and, very rarely, melanomas.

As for histology, squamous (epidermoid) carcinoma type I, well differentiated corresponds to about 70% or 80% of the cases. According to the Broders' classification, the risk of involvement of the inguinal lymph nodes ranges from 0% to 48% for type I tumors [40]. Knowledge on these histopathological aspects is of paramount importance in therapeutic planning, as well as in patients' prognosis. A recent study [10] confirms the importance of tumor classification and staging to help professionals in treatment planning, provide a prognosis indication, allow assessing treatment outcomes, and also contribute to ongoing research on this disease.

In relation to cases of positive metastasis and their correlation with age, a higher prevalence of metastasis was observed among individuals ≥ 60 years, something which may be related to the time of exposure to disease and/or the time elapsed to start the treatment. A study indicated that 15% to 50% of the patients with penile lesions seek care one year after the onset of early symptoms [12]. The occurrence of distant metastasis cases are uncommon in patients with penile cancer, observed in about 3% to 5% of the cases. Usually, hematogenous metastases occur late in the disease course and they are associated with poor prognosis [20].

Partial penectomy was the most frequent type of treatment, adopted in 67% of the individuals analyzed. Surgical treatment, with amputation, is

INTERNATIONAL ARCHIVES OF MEDICINE
SECTION: EPIDEMIOLOGY
ISSN: 1755-7682

2017

Vol. 10 No. 223
doi: 10.3823/2493

the technique traditionally used in penile cancer, particularly effective in tumors whose local recurrence rate is ≤ 8%. In tumors ≥ 4 cm, as well as in invasive tumors of the corpora cavernosa or urethra, the procedure indicated is partial or total penectomy [25]. On the other hand, due to the nature of mutilation, efforts have been made to find alternatives that replace conventional surgical treatment, e.g. the micrographic surgery proposed by Mohs, radiotherapy, laser treatment, and cryosurgery [41]. The most significant foundation when using these resources is the complete excision or destruction of the primary tumor [17].

Another factor to consider is the association of smoking with penile cancer, this risk factor is highlighted because among smokers the occurrence of penile cancer increases about 3 to 4.5 times. Men who smoke > 10 cigarettes a day have a 1.14-fold increased risk when compared to those who do not smoke. In some cultures, such as those in rural Brazilian municipalities, there is a habit of chewing tobacco, a factor that increases the risk of penile cancer by 2.11 times [5, 8]. Among the 305 patients analyzed in this study, smoking as a risk factor occupied the 3rd position, indicating that 53.4% are tobacco users. This risk factor has to be analyzed more deeply, although the association between smoking and carcinoma has been reported, but it remains unclear which is the tobacco action mechanism in penile carcinogenesis [34-36].

Conclusion

Analyzing the profile of patients who have undergone penectomy allowed us to conclude that most of them were elderly, had low schooling and family income of up to 5 minimum wages, and they lived or came from municipalities outside the Metropolitan Region of Recife.

This study showed that hygiene care, smoking cessation, and surgical correction of phimosis seem to be of paramount importance among the preventive actions of penile cancer, since they prevail as risk factors among the individuals under study.

Considering that absence or deficiency of information obstructs and hinders the adoption of behaviors that consolidate actions to promote health and prevent health problems, there is a need to stimulate activities aimed at health education, focused on developing knowledge and attitudes that help individuals make choices and make decisions that fit their health, in order to prevent, among other diseases, penile cancer and to promote the search for health care in the face of early changes that may lead to penile neoplasms.

References

1. World Cancer Research Fund International. Recommendations for cancer prevention [Internet]. 2012 [cited 2012 Mar 12]. Available from: http://www.wcrf.org
2. Instituto Nacional de Câncer. Incidência de câncer no Brasil [Internet]. 2008 [cited 2012 Apr 21]. Available from: http://www.inca.gov.br
3. Garófolo A, Avesani CM, Camargo KG, Barros ME, Silva SRJ, Taddei JAAC, et al. Dieta e câncer: um enfoque epidemiológico. Rev Nutr. 2004; 17:492-3.
4. Guerra MR, Gallo CVM, Azevedo G, Mendonça S. Risco de câncer no Brasil: tendências e estudos epidemiológicos mais recentes. Rev Bras Cancerol. 2005; 51:227-34.
5. Pow-Sang MR, Ferreira U, Pow-Sang JM, Nardi AC, Destefano V. Epidemiology and natural history of penile cancer. Urology. 2010; 76:S2-S6.
6. Misra S, Chaturvedi A, Misra NC. Penile carcinoma: a challenge for the developing world. Lancet Oncol. 2004; 5:240-7.
7. Souza KW, Reis PED, Gomes IP, Carvalho EC. Estratégias de prevenção para câncer de testículo e pênis: revisão integrativa. Rev Esc Enferm USP. 2011; 45:277-82.

8. Carvalho NS, Kannenberg AP, Munaretto C, Yoshioka D, Absy MCV, Tambara Filho R. Associação entre HPV e câncer peniano: revisão de literatura. DST J Bras Doenças Sex Transm. 2007; 19:92-5.

9. Favorito LA, Nardi A, Ronalsa M, Zequi SC, Sampaio FJB, Glina S. Epidemiologic study on penile cancer in Brazil. Int Braz J Urol. 2008; 34:587-93.

10. Reis AAS, Paula LB, Paula AAP, Saddi VA, Cruz AD. Clinico-epidemiological aspects associated with penile cancer. Ciênc Saúde Coletiva. 2010; 15:1105-11.

11. Paula AAP, Almeida NJC, Cruz AD, Freitas Jr R. Penile squamous carcinoma: epidemiological, histopathological, viral influence and surgical considerations. Rev Bras Cancerol. 2005; 51:243-52.

12. Barocas DA, Chang SS. Penile cancer: clinical presentation, diagnosis, and staging. Urol Clin North America. 2010; 37:343-52.

13. Brasil. Política Nacional Integral de Atenção à Saúde do Homem. Brasília (DF): Ministério da Saúde; 2008.

14. Cubilla AL. The role of pathologic prognostic factors in squamous cell carcinoma of the penis. World J Urol. 2009; 27(2):169-77.

15. Guimarães GC, Lopes A, Campos RSM, Zequi SC, Leal MLO, Carvalho AL, et al. Front pattern of invasion in squamous cell carcinoma of the penis: new prognostic factor for predicting risk of lymph node metastases. Urology. 2006; 68:148-53.

16. Guimarães CG, Cunha IW, Soares FA, Lopes A, Torres J, Chaux A. Clinicopathological features, nodal metastasis and outcome according to WHO classification of penile squamous cell carcinoma: a report of 333 cases. J Urol. 2009; 182:528-34.

17. Sociedade Brasileira de Urologia, Associação Médica Brasileira, Conselho Federal de Medicina. Projeto diretrizes: carcinoma do pênis, parte I. Brasília (DF): SBU; 2006.

18. Lynch BF, Pettaway CA. Tumors of the penis. In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ, Kavoussi LR, Novick AC. Campbell's urology. Philadelphia (PA): Saunders; 2002. p. 2945-82.

19. Pompeo ACL, Billis A. Carcinoma epidermoide do pênis. Uroptologia: pênis. Int Braz J Urol. 2003; 29:44-50.

20. Heyns CF, Valdés AM, Pompeo ACL. Diagnosis and staging of penile cancer. J Urol. 2010; 76(2 Suppl 1):S15-S23.

21. Engels EA, Pfeiffe RM, Goedert JJ. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS. 2006; 20:1645-54.

22. Ravizzini GC, Wagner M, Borges-Neto S. Positron emission tomography detection of metastatic penile squamous cell carcinoma. J Urol. 2000; 165:1633-4.

23. Lima MVA, Tavares JM, Silveira RA, Tomás Filho ME, Silva FA, Silva LFG. Intra operative use of gama probe for identification of sentinel node in penile cancer. Int Braz J Urol. 2002; 28:123-9.

24. Minhas S, Manseck A, Watya S, Hegarty PK. Penile cancer: prevention and premalignant conditions. Urology. 2010; 76:24-35.

25. Gil AO, Pompeo ACL, Sarkis AS, Matsuo M, Motta THB, Arap S. Evaluation of the influence of protein p53 in penile carcinoma. Int Braz J Urol. 2002; 28:33-9.

26. Ficarra V, Zattoni F, Artibani W. Nomogram predictive of pathological inguinal lymph node involvement in patients with squamous cell carcinoma of the penis. J Urol. 2006; 175:1700-5.

27. Bleeker MCG, Heideman DAM, Snijders PJF, Horemblas S, Dillner J, Meijer CJLM. Penile cancer: epidemiology, pathogenesis and prevention. World J Urol. 2009; 27:141-50.

28. Salvioni R, Necchi A, Piva L, Colecchia M, Nicolai N. Penile cancer. Urol Oncol. 2009; 27:677-85.

29. Daling JR, Madeleine MM, Johnson LG. Penile cancer: importance of circumcision, human papillomavirus and smoking in situ and invasive disease. Int J Cancer. 2005; 116:606-16.

30. Ferrándiz-Pulido C, Torres I, García-Patos V. Penile squamous cell carcinoma. Actas Dermo-Sifiliográficas. 2012; 103:478-87.

31. Chaux A, Pfannl R, Lloveras B, Alejo M, Clavero O, Lezcano C. Distinctive association of 16INK4a overexpression with penile intraepithelial neoplasia depicting wart and/or basaloid features: a study of 141 cases evaluating a new nomenclature. Am J Surg Pathol. 2010; 34:385-92.

32. Austin PF. Circumcision. Curr Opin Urol. 2010; 20:318-22.

33. Burgu B, Aydogdu O, Tangal S, Soygur T. Circumcision: pros and cons. Indian J Urol. 2010; 26:12-5.

34. Hellberg D, Valentin J, Eklund T, Nilsson S. Penile cancer: is there an epidemiological role for smoking and sexual behavior? Br Med J. 1987; 295:1306-8.

35. Maden C, Sherman KJ, Beckmann AM. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. J Natl Cancer Inst. 1993; 85:19-24.

36. Harish K, Ravi R. The role of tobacco in penile carcinoma. Br J Urol. 1995; 75:375-7.

37. Sous AR, Pérez-Utrilla M, Aguilera BA, Tabernero GJ, Cisneros L, Barthel JP. A review of penile cancer. Adv Urol. 2009; (2009):[about 3 screens].

38. Ornellas AA, Brown GA. Câncer urológico (câncer de pênis). In: Ferreira CG, Rocha JC. Oncologia molecular. São Paulo: Atheneu; 2004. p. 224-9.

39. Micali G, Nasca MR, Innocenzi D, Schwartz RA. Penile cancer. J Am Acad Dermatol. 2006; 54:369-91.

40. Solsona E, Bahl A, Brandes SB, Dickerson D, Puras-Baez A, Van Poppel H, et al. New developments in the treatment of localized penile cancer. Urology. 2010; 76:36-42.

41. Kople LFF, Gouvêa OS, Bastos JCF. Dez anos de experiência com cirurgia micrográfica pelo método de Munique: relato de 93 casos operados. An Bras Dermatol. 2005; 80:583-90.