Histopathology

Histopathology 2023 DOI: 10.1111/his.14927

Metastatic solid tumours to the penis: a clinicopathologic evaluation of 109 cases from an international collaboration

Luiz M. Nova-Camacho,[1] Katrina Collins,[2] Kiril Trpkov,[3] Andres M. Acosta,[4] Ankur R. Sangoi,[5] Mahmut Akgul,[6] Angela Chou,[7] Antonio Polonia,[8] Ângelo Rodrigues,[9] Asli Yilmaz,[3] Delia Perez-Montiel,[10] Fiona Maclean,[11] Francisco Javier Queipo Gutiérrez,[12] Félix Contreras,[13] Howard H. Wu,[2] Isabel Alvarado-Cabrero,[14] Inés de Torres,[15] Irune Ruiz,[1] João Lobo,[9,16,17] Susan Prendeville,[18] Manuel Manrique Celada,[1] Liang Cheng,[19] Laurence A. Galea,[20] Michael Hwang,[2] Manju Aron,[21] María García-Martos,[22] Nicole Zalles,[23] Maria Rosaria Raspollini,[24] Sean R. Williamson,[23] Thomas M. Ulbright[2] & Angel Panizo[25]

[1]*Department of Pathology, Donostia University Hospital, San Sebastian, Spain,* [2]*Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA,* [3]*Department of Pathology and Laboratory Medicine, University of Calgary, Calgary, AB, Canada,* [4]*Department of Pathology, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA,* [5]*Department of Pathology, El Camino Hospital, Mountain View, CA,* [6]*Department of Pathology and Laboratory Medicine, Albany Medical Center, Albany, NY, USA,* [7]*Department of Anatomical Pathology, Royal North Shore Hospital and University of Sydney, Sydney, NSW, Australia,* [8]*Ipatimup—Institute of Molecular Pathology and Immunology, University of Porto,* [9]*Department of Pathology, Portuguese Oncology Institute of Porto, Porto, Portugal,* [10]*Department of Pathology, Instituto Nacional de Cancerología, Mexico City, Mexico,* [11]*Department of Pathology and Laboratory Medicine, Douglass Hanly Moir Pathology, Sonic Healthcare, Sydney, NSW, Australia,* [12]*Department of Pathology, University Hospital of A Coruña, A Coruña, Spain,* [13]*Laboratorio de Patología, Clínica Universitaria Unión Médica, PUCMM, Santiago, Dominican Republic,* [14]*Department of Pathology Oncology, Star Medica Hospital, Oncology Hospital, IMSS, Mexico City, Mexico,* [15]*Department of Pathology, Vall d'Hebron Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain,* [16]*Cancer Biology and Epigenetics Group, IPO Porto Research Center (GEBC CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto) & Porto Comprehensive Cancer Center (P.CCC),* [17]*Department of Pathology and Molecular Immunology, Institute of Biomedical Sciences Abel Salazar, University of Porto (ICBAS-UP), Porto, Portugal,* [18]*Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada,* [19]*Department of Pathology and Laboratory Medicine, Brown University Warren Alpert Medical School, Lifespan Academic Medical Center, and the Legorreta Cancer Center at Brown University, Providence, RI, USA,* [20]*Department of Anatomical Pathology, Melbourne Pathology, Sonic Healthcare, Dandenong, Vic., Australia,* [21]*Department of Pathology and Laboratory Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA,* [22]*Department of Pathology, Gregorio Marañon University Hospital, Madrid, Spain,* [23]*Department of Pathology and Laboratory Medicine, Cleveland Clinic, Cleveland, OH, USA,* [24]*Histopathology and Molecular Diagnostics, Careggi University Hospital, Florence, Italy and* [25]*Department of Pathology, University Hospital of Navarra, Pamplona, Spain*

Date of submission 9 February 2023
Accepted for publication 1 April 2023

Address for correspondence: Luiz M. Nova-Camacho, Department of Pathology, Donostia University Hospital, Begiristain Doktorea Pasealekua, s/n, 20014 San Sebastian, Spain. e-mail: luismi_15_16@hotmail.com

This work has been presented as a poster during the United States & Canadian Academy of Pathology's 112th Annual Meeting, March 11–16, 2023, in New Orleans, Louisiana. (Poster Session on Wednesday, March 15, 2023, from 9:30 AM to 12:00 PM at the New Orleans Ernest N. Morial Convention Center in Exhibit Hall B.)

Nova-Camacho L M, Collins K, Trpkov K, Acosta A M, Sangoi A R, Akgul M, Chou A, Polonia A, Rodrigues Â, Yilmaz A, Perez-Montiel D, Maclean F, Queipo Gutiérrez F J, Contreras F, Wu H H, Alvarado-Cabrero I, de Torres I, Ruiz I, Lobo J, Prendeville S, Manrique Celada M, Cheng L, Galea L A, Hwang M, Aron M, García-Martos M, Zalles N, Raspollini M R, Williamson S R, Ulbright T M & Panizo A
(2023) *Histopathology*. https://doi.org/10.1111/his.14927

Metastatic solid tumours to the penis: a clinicopathologic evaluation of 109 cases from an international collaboration

Aims: To elucidate the spectrum of metastatic tumours to the penis and their clinicopathologic features.
Methods: The databases and files of 22 pathology departments from eight countries on three continents were queried to identify metastatic solid tumours of the penis and to characterize their clinical and pathologic features.
Results: We compiled a series of 109 cases of metastatic solid tumours that secondarily involved the penis. The mean patient age at diagnosis was 71 years (range, 7–94 years). Clinical presentation commonly included a penile nodule/mass (48/95; 51%) and localised pain (14/95; 15%). A prior history of malignancy was known in 92/104 (89%) patients. Diagnosis was made mainly on biopsy (82/109; 75%), or penectomy (21/109; 19%) specimens. The most common penile locations were the glans (45/98; 46%) and corpus cavernosum (39/98; 39%). The most frequent histologic type was adenocarcinoma (56%). Most primary carcinomas originated in the genitourinary (76/108; 70%) and gastrointestinal (20/108; 18%) tracts, including prostate (38/108; 35%), urinary bladder (27/108; 25%), and colon/rectum (18/108; 17%). Concurrent or prior extrapenile metastases were identified in 50/78 (64%) patients. Clinical follow-up (mean 22 months, range 0–171 months) was available for 87/109 (80%) patients, of whom 46 (53%) died of disease.
Conclusion: This is the largest study to date of metastatic solid tumours secondarily involving the penis. The most frequent primaries originated from the genitourinary and gastrointestinal tracts. Metastatic penile tumours usually presented with penile nodules/masses and pain, and they often occurred in the setting of advanced metastatic disease, portending poor clinical outcomes.

Keywords: metastasis, penile, penis, secondary tumours

Introduction

Penile cancer is an uncommon malignancy with a reported incidence of less than one case per 100,000 in Europe and the United States.[1] The most common primary penile carcinoma is squamous cell carcinoma, and the risk factors include lack of circumcision, phimosis, chronic inflammation, smoking, radiotherapy, ultraviolet radiation, human papillomavirus infection, lichen sclerosus, and possibly lichen planus.[2–4]

Metastases to the penis, however, are rare and are associated with disseminated disease and poor prognosis. Approximately 75% of penile metastases originate from the genitourinary tract, with the most common primary site being urinary bladder and prostate.[5–13]

In 1870, Eberth[7] first described a case of penile metastasis. Since then, this topic has been mostly a subject of case reports and small case series, or review articles.[5–13] Thus far, the largest cohorts of secondary solid malignancies to the penis have been compiled by Chaux *et al.*[6] in 2011 and by Hizli *et al.*[5] in 2006, which included 17 and 10 cases, respectively.

In this study, we evaluated a large multiinstitutional series of metastatic solid tumours to the penis, focusing primarily on their clinicopathologic features and outcomes.

Material and Methods

The databases and files of 22 pathology departments from eight countries on three continents, which also included several large tertiary and quaternary referral centers, were queried to identify metastatic solid tumours to the penis. All available clinical and pathologic data were obtained by reviewing the medical

records and the pathology reports and/or glass slides. This was carried out by individual pathologists in their own departments. No central review was performed, nor were data obtained from photographs alone. Medical records and pathology reports were reviewed to obtain clinical data that included: age, clinical presentation, prior history of malignancy, metastases at other sites, interval time between primary tumour and metastasis, interval between metastasis and last follow-up, and the status at last follow-up. Pathology reports and/or available slides of the penile metastases were reviewed to collect the following information: specimen type, tumour size, penile location(s), histologic type, primary site, tumour emboli or lymphovascular invasion (LVI), results of diagnostic immunohistochemical work-up, and/or results of molecular studies (when available). Representative macroscopic and microscopic images were obtained from the corresponding pathologists.

All data were compiled in a Microsoft Excel (2019) (Microsoft, Redmond, WA, USA) spreadsheet and analysed using both Microsoft Excel (2019) software and IBM SPSS statistic for macOS software version 29.0 (IBM, Armonk, NY, USA).

Results

One hundred and nine patients were included in the study, including one previously reported case.[12] Glass slides were rereviewed to obtain pathologic data in 90 cases; while in the remaining 19 cases, data were obtained solely from medical records and pathology reports.

The mean age at diagnosis was 71 years (range, 7–94 years). Of note, only 2/109 (2%) patients were under the age of 40 years, including a 7-year-old boy with an epithelioid sarcoma of the sacrum and a 39-year-old man with a teratoma of the testis. A detailed oncologic history was available for 104/109 patients. Of those with available clinical history, 92 (88%) patients had a known prior or concurrent malignancy; in the remaining 12 (12%), the penile involvement was the initial clinical manifestation of the disease. However, all of these 12 patients received a diagnosis of the primary cancer during the follow-up.

Information regarding the clinical presentation was available for 96/109 (88%) patients, of whom 95/96 (99%) had either a mass/nodule (48/95; 51%), localised pain (14/95; 15%), hematuria (11/95; 12%), ulceration (5/95; 5%), edema (4/95; 4%), lower urinary tract symptoms (4/95; 4%), swollen penis (2/95; 2%), and/or others (abscess, penile induration, urethral stricture, or thickened edge of the corona; 5/95; 5%), with priapism in 2/95 (2%) patients. In 1/96 (1%), penile involvement was discovered incidentally on physical examination. Some patients, however, had multiple symptoms/signs at presentation (32/95; 32%). A summary of the demographics and clinical presentations are shown in Table 1.

Table 1. Summary of demographics and clinical presentations

Characteristics	Total (%)
Number of patients	109
Mean/median age (years)	71/71
Prior history of cancer	104
Yes	92 (88)
No	12 (12)
Clinical manifestation of disease	96
Yes	95 (99)
No	1 (1)
Clinical presentation	96
Mass/nodule	48 (51)
Pain	14 (15)
Hematuria	11 (12)
Ulceration	5 (5)
Edema	4 (4)
Lower urinary tract symptoms	4 (4)
Swollen penis	2 (2)
Priapism	2 (2)
Others[1]	5 (5)

[1]Other symptoms/signs at presentation included abscess, penile induration, urethral stricture, or thickened edge of corona.

The diagnosis was made on a broad range of specimen types that included biopsy (82/109; 75%), either incisional (68) or excisional (14); penectomy (21/109; 19%), either partial (8), total (7), or unspecified (6); fine-needle aspiration (FNA) (4/109; 4%); urethrectomy (1/109; 1%); and circumcision (1/109; 1%).

The mean tumour size of the penile metastases was 2.4 cm (range, 0.3–10.6 cm). The location of the penile metastases was specified in 98/109 (90%) patients. Glans penis was affected in 45/98 (46%) cases [either alone in 32/98 (33%) or as part of a multifocal lesion in 13/98 (13%)]. Corpus cavernosum was involved in 39/

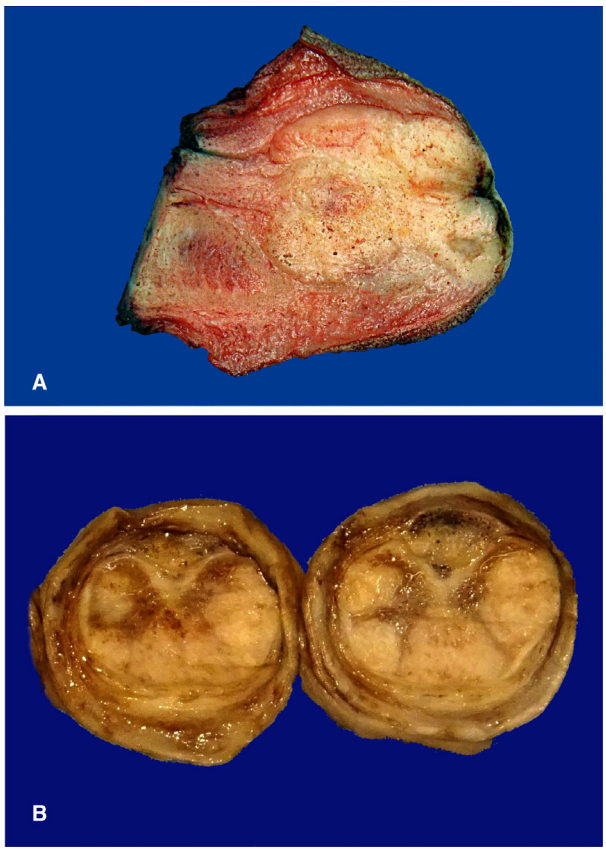

Figure 1. Macroscopic images of metastatic solid tumours to the penis. A: Partial penectomy specimen with metastasis from prostatic adenocarcinoma. The tumour involves the glans penis, penile urethra with extension into corpus spongiosum. B: Partial penectomy with metastasis from rectal adenocarcinoma. The tumour involves corpus cavernosa.

98 (39%) cases [either alone in 20/98 (20%) or as part of a multifocal lesion in 19/98 (19%)], as illustrated in Figure 1. Other locations included the proximal penile root in 12/98 (12%) patients, the shaft in 10/98 (10%), and the foreskin in 5/98 (5%) cases.

The primary site of malignancy was identified in 108/109 (99%) patients. The most common primaries originated in the genitourinary tract (76/108, 70%), followed by the gastrointestinal tract (20/108, 18%), and the respiratory tract (4/108, 4%). Other uncommon primaries included the skin (3/108, 3%), skeletal system (1/108, 1%), and the bone marrow (1/108, 1%). The primary site was unknown in 2/108 (2%) cases, and one patient had multiple primaries, and the primary site could not be clarified with confidence.

Within the genitourinary system, the most frequent primary organ was the prostate (38/108; 35%), followed by the urinary bladder (27/108; 25%), kidney (7/108; 6%), testis (2/108; 2%), and urethra (2/108; 2%). Within the gastrointestinal tract, the most frequent primary location was the colon/rectum (18/108; 17%), followed by the oesophagus (1/108; 1%) and the stomach (1/108; 1%). Lastly, the lung (4/108; 4%) was the only primary organ within the respiratory tract. The primary sites of metastatic solid tumours to the penis are shown in Table 2.

Table 2. Primary sites of metastatic solid tumors to the penis (n = 106)[1]

Primary site	n (%)
Prostate	38 (36)
Bladder	27 (25)
Colon/rectum	18 (17)
Kidney	7 (7)
Lung	4 (4)
Skin (right toe, dorsal, perianal)	3 (3)
Testis	2 (2)
Urethra	2 (2)
Esophagus	1 (1)
Sacrum	1 (1)
Stomach	1 (1)
Bone marrow	1 (1)
Not defined[2]	1 (1)

Numbers are rounded up to the integer value.
[1]n = 106, unknown site in two cases (2%).
[2]Not defined, the patient had a history of two primary malignancies.

The most frequent histologic type was carcinoma (101/109; 93%), including adenocarcinoma (61/109; 56%) [mostly from prostatic (36), or colorectal (18) primaries], urothelial carcinoma (27/109; 25%), renal cell carcinoma (RCC), (6/109; 6%), [clear cell RCC (4), papillary RCC (1) and RCC, not otherwise specified (NOS) (1)], neuroendocrine carcinoma (4/109; 4%), and poorly differentiated carcinoma (3/109; 3%). Other less common primaries included malignant melanoma (3/109; 3%), sarcoma (2/109; 2%), teratoma (1/109; 1%), plasma cell myeloma/multiple myeloma (1/109; 1%), and yolk sac tumour (1/109; 1%). Of the three poorly differentiated carcinomas, one case originated in the bladder and two cases had an unknown primary. The various histologies of metastatic tumours to the penis are shown in Table 3, and

Table 3. Histologic types of metastatic solid tumors to the penis (n = 109)

Histologic type	n (%)
Carcinoma	101 (93)
Adenocarcinoma	61 (56)
Urothelial carcinoma	27 (25)
Renal cell carcinoma (clear cell, papillary, and NOS)	6 (6)
Neuroendocrine carcinoma (small cell and large cell)	4 (4)
Poorly differentiated carcinoma	3 (3)
Malignant melanoma	3 (3)
Sarcoma	2 (2)
GIST	1 (1)
Epithelioid sarcoma	1 (1)
Teratoma	1 (1)
Plasma cell myeloma/multiple myeloma	1 (1)
Yolk sac tumor	1 (1)

Numbers are rounded up to the integer value.
GIST, gastrointestinal stromal tumor; NOS, not otherwise specified.

representative microscopic images are illustrated in Figures 2 and 3.

Ancillary studies, including immunohistochemistry (IHC) and/or molecular tests, were performed as part of the initial diagnostic work-up in 79/93 (85%) cases. In the remaining 14 (15%) cases, the diagnosis of penile metastasis was made on morphology and considering the relevant clinical history. In 13 out of the latter 14 (93%) cases, the patients had a prior history of malignancy, except in a 74-year-old patient with urothelial carcinoma of the bladder that was unknown at the time of the diagnosis of the penile metastasis. The main IHC panels that were used to confirm the diagnosis of the primary site are listed in Table 4.

Tumour emboli or LVI were identified in 43/100 (43%) cases, including three with extensive LVI. Data on metastases to other sites were available for 78/109 (72%) patients, of which 50/78 (64%) had concurrent or prior extrapenile metastases. In this group, 23/50 (46%) patients had a metastasis only in one extrapenile site and 27/50 (54%) patients had metastases involving two or more extrapenile sites.

The time interval from the diagnosis of the primary tumour to the detection of the penile metastasis was known for 84/109 (73%) patients. The mean and median time intervals between the primary diagnosis and the occurrence of penile metastases were 39 and 29 months, respectively (range, 0–156 months). In 10/84 (12%) patients, the penile metastasis occurred synchronously with the primary tumour. In 42/84 (50%) patients, the penile metastasis developed within the first 3 years since the initial diagnosis, and in 32/84 (34%) patients longer than 3 years, as shown in Table 5.

Follow-up data were available for 87/109 (80%) patients. Of these, 46/87 (53%) patients died of disease, 28/87 (32%) patients were alive with disease, 3/87 (3%) patients died without disease, and 10/87 (11%) died of unknown causes.

Discussion

Although various aspects of this topic have been studied previously, to our knowledge the current study represents the largest and the most detailed series on metastatic solid tumours of the penis. We found that most metastatic solid tumours to the penis originate in the genitourinary and the gastrointestinal tracts. Metastatic penile tumours usually present with penile masses and pain, most commonly involving the glans penis and the corpus cavernosum. Penile metastases often occur in the setting of advanced metastatic disease and are associated with poor prognosis.

A small case series performed in 2000 by Dutt *et al.*[14] described five cases of penile metastases diagnosed in patients with disseminated disease at autopsy, including primary tumours from the pancreas (two) urinary bladder (two), and prostate (one). In 2012, Chaux *et al.*[6] described 17 cases of metastatic solid tumours to the penis, the majority of which either presented with a penile mass or priapism. The primary sites were urinary bladder (six), prostate (four), colon/rectum (two), lung (two, one with squamous cell carcinoma and one with small cell carcinoma), base of the tongue (one), skin (one), and bone marrow (one).

In a literature review performed in 2012 by Mearini *et al.*,[8] ~500 cases of penile metastases were identified. Patient age at presentation ranged between 60 and 80 years, with about 60% of the patients showing symptoms associated with penile nodules, while priapism was reported with varying frequency (20%–53%). Most of the metastatic lesions originated from the adjacent genitourinary and pelvic organs, mainly the urinary bladder, prostate, rectum, and sigmoid colon. Most of the cases they reviewed, when synchronous, were often associated with disseminated disease and had poor outcome. More recently, a retrospective study carried out by Ellis and Epstein[13] reported 29

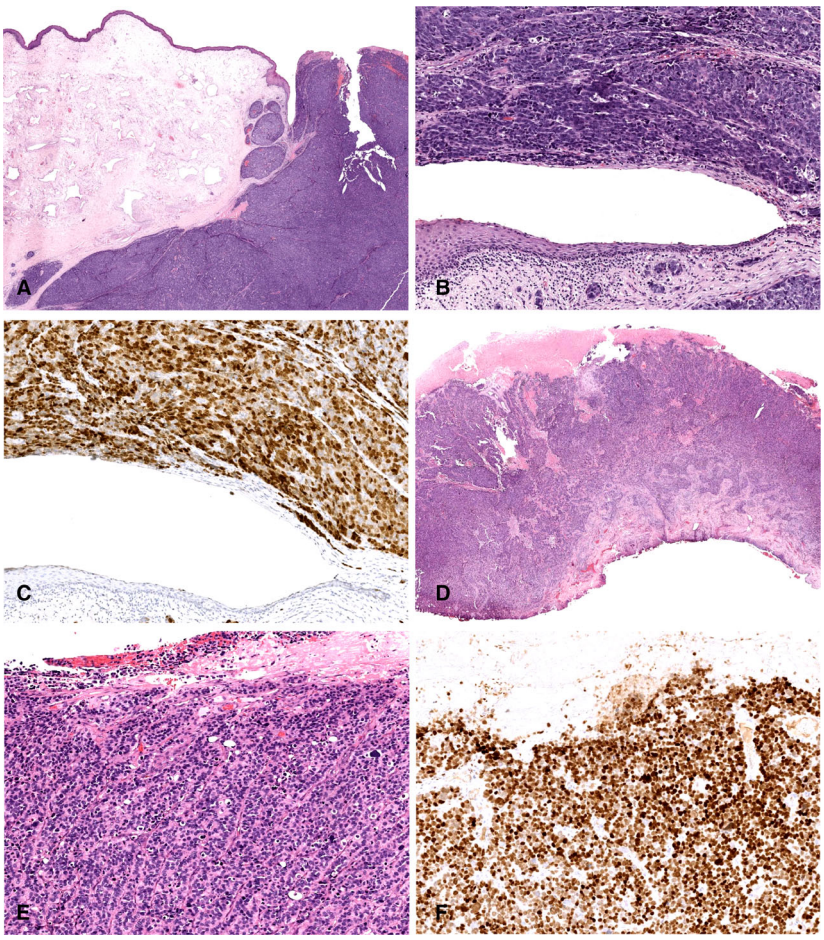

Figure 2. Microscopic images of metastatic solid tumours to the penis. A–C: High-grade adenocarcinoma of the prostate with nuclear positivity for NKX3.1 immunostain. D–F: Urothelial carcinoma from the urinary bladder with nuclear positivity for GATA3 immunostain.

cases of penile metastasis from prostatic adenocarcinoma during a 20-year period. The mean age of the patients was 75 years. Nineteen of the 29 patients had a prior history of prostatic adenocarcinoma, and 16/29 (55%) showed ductal features in the metastasis. Interestingly, of the 8/19 (42%) patients whose primary prostatic adenocarcinoma showed ductal features, seven had ductal features in the penile metastasis, leading to the conclusion that penile involvement by prostatic adenocarcinoma displays ductal features considerably more frequently than prostatic adenocarcinoma in general. In the current study, of the 38 cases of prostatic adenocarcinomas, 34 were acinar adenocarcinomas, two were neuroendocrine carcinomas, and there were one case each of poorly differentiated adenocarcinoma and ductal adenocarcinoma.

Several additional reports have documented metastases of diverse tumour types and various tumour sites, including adenocarcinoma of the pancreas, small cell carcinoma and adenosquamous cell carcinoma of the prostate, squamous cell carcinoma of the tongue, malignant melanoma of the skin, follicular thyroid carcinoma, adenocarcinoma of the seminal vesicle, squamous carcinoma of the oesophagus, glomangiosarcoma, and seminoma.[6,13,15–21]

Although the penis is very rich in blood vessels and lymphatics, metastatic tumours to it are exceedingly rare. According to the previous reports, the penile metastasis usually represented a late manifestation of widespread disease.[6,8,10,14,15]

Previous data indicated that penile metastases typically occur in older patents; similarly, this was evident also in the current study, as both mean and median age at presentation was 71 years.[8] Only two patients were younger than 40 years (7 and 39 years); however, both had a prior history of malignancy and presented with clinical manifestation of disease (swollen penis and

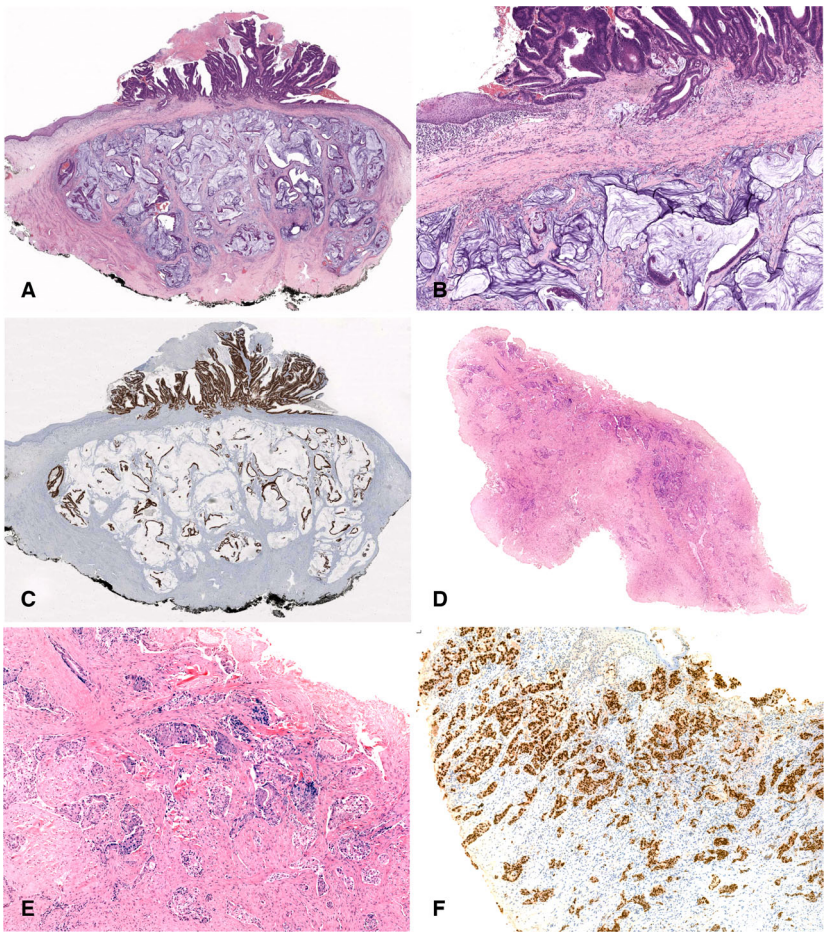

Figure 3. Microscopic images of metastatic solid tumours to the penis. A–C: Colorectal adenocarcinoma with mucinous features, with nuclear positivity for CDX2 immunostain. D–F: Adenocarcinoma of the lung with nuclear positivity for TTF1 immunostain.

penile mass, respectively). The first died from disease (at 13 months) and the other was alive with disease at the last follow-up (at 16 months). Thus, a detailed clinical evaluation is required in all patients with previous malignancies who present with penile symptoms.

Penile metastases are commonly identified in patients with known malignancies.[8,10,14] Accordingly, 88% of the patients in our series had a known malignancy, whereas penile metastasis was the initial manifestation in the remaining 12%. Of the 12 patients with unknown prior malignancies, three had prostatic adenocarcinomas, three had bladder urothelial carcinomas, two had colorectal adenocarcinoma, one had RCC, NOS, one had lung adenocarcinoma, and two had unknown primary carcinoma.

Priapism is defined as a prolonged erection lasting more than 6 hr in the absence of sexual stimulation.[22] Malignant priapism is a term first used by Peacock[23] in 1938, denoting an invasion of malignant cells into the cavernous sinuses and associated venous systems. In the previous reports, this phenomenon was a common clinical finding in patients with penile metastases, and its frequency varied from 20% to 53%.[8,24] Such a high frequency in the previous reports may stem from a selection bias inherent in smaller studies. In the present study, however, only 2% of the patients had priapism as a presenting symptom, which may be an underestimation. In our view, however, this is likely a more realistic estimation of the true frequency based on a more detailed pathologic evaluation from a larger multiinstitutional cohort.

Generally, the diagnosis of metastatic solid tumours to the penis was made either on biopsy or on FNA.[10,11,25,26] However, cases diagnosed on penectomy specimens or autopsy have also been reported.[5,8] In the present series, most of the penile metastases were diagnosed on biopsies (75%), whereas penectomy was the method of diagnosis in 19%, and FNA in 4% of the cases.

Table 4. Main immunohistochemical panels used to confirm the diagnosis of the most frequent primary tumors in this series

Primary site	Stain
Prostatic adenocarcinoma	NKX3.1, PSA, PSMA
Urothelial carcinoma	GATA3, p40, p63
Colorectal carcinoma	Keratin 20, CDX2, SATB2
Renal cell carcinoma (clear cell, papillary, and NOS)	PAX-8, CA IX, keratin 7, AMACR
Lung adenocarcinoma	Keratin 7, TTF1, napsin A
Neuroendocrine carcinoma	Synaptophysin, chromogranin
Malignant melanoma	S100, MelanA, HMB45
GIST	CD34, KIT, DOG1

AMACR, Alpha-methylacyl-CoA racemase; CA IX, carbonic anhydrase IX; CDX2, caudal type homeobox 2; DOG1, discovered on GIST-1; GATA3, GATA binding protein 3; GIST, gastrointestinal stromal tumor; NKX3.1, NK3 homeobox 1; NOS, not otherwise specified; PAX8, paired box gene 8; PSA, prostatic specific antigen; PSMA, prostatic specific membrane antigen; SATB2, SATB homeobox 2; TTF1, thyroid transcription factor 1.

Table 5. Time interval between the primary tumor and penile metastasis (n = 84)

Months (years)	n (%)
0/synchronous	10 (12)
1–12 (1)	20 (24)
13–36 (3)	22 (26)
37–60 (5)	11 (13)
61–120 (10)	18 (21)
>121 (>10)	3 (4)

According to prior studies, ~70% of the metastases involved both corpora cavernosa and only 15% were unilateral. Corpus spongiosum and glans penis were affected in 10% of cases each, and the prepuce in about 5%.[8] In the present study, the most common locations were glans penis (46%) and corpora cavernosa (39%).

In this study, the most common primary site of penile metastases was the prostate (35%), followed by the urinary bladder (25%), and the colon/rectum (17%), findings in line with previous studies.[6,8,14]

Most common histologic types of primary malignancies reported previously were urothelial carcinoma and prostatic adenocarcinoma.[5,6] In the present study, the most frequent types were carcinoma (93%), followed by melanoma (3%), and sarcoma (2%). Among carcinomas, the most frequent histologic subtypes were adenocarcinoma (56%), urothelial carcinoma (25%), RCC (6%), and neuroendocrine carcinoma (4%). Although urothelial carcinomas can arise from any part of the urethra, including the distal penile urethra, none of the cases included in this study were found to have carcinoma *in situ* or papillary urothelial carcinoma, arising solely from the urethra. All patients were also found to have a distinct primary malignancy during follow-up, thus confirming the metastatic nature of the lesions.

Tumour emboli or LVI were identified in 43% of cases in the current study. It is thought that the most common mode of penile involvement is by retrograde venous spread. Other routes include the lymphatic system, arteries, direct extension, or iatrogenic implantation.[8]

Finally, in patients with available follow-up, 53% died of disease. This is also in accordance with the previous data that show poor prognoses for patients with penile metastases, as most have disseminated disease, are in poor general health, and die within a year of the presentation.[8,10]

In conclusion, we describe the largest and the most detailed series compiled to date of metastatic solid tumours to the penis, which further extends our understanding of the clinical and pathologic features and outcomes of patients harbouring secondary penile tumours. We found that most patients presented with clinical manifestations of disease in the context of a known primary malignancy and/or disseminated disease and had poor outcomes. The most frequent primary sites were in the genitourinary and gastrointestinal tracts, specifically the prostate, followed by the urinary bladder and the colorectum. The most frequent histologic types of penile metastasis were adenocarcinoma and urothelial carcinoma.

Author contributions

Concept, design, and coordination: LMNC, AP; contribution of cases: all authors; histopathological evaluation: all authors; analysis of clinical, and histopathologic data: LMNC; article draft: LMNC, KC, KT; intellectual contributions: all authors; article editing: all authors.

Conflict of interest

The authors have no conflicts of interest to disclose.

Ethics approval/consent to participate

This was a retrospective study not interfering with diagnosis and patient management.

Data availability statement

The data generated in this study are available from the corresponding author upon request.

References

1. Van Poppel H, Watkin NA, Osanto S *et al*. Penile cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 2013; **24**; vi115–vi124.
2. Misra S, Chaturvedi A, Misra NC. Penile carcinoma: a challenge for the developing world. *Lancet Oncol.* 2004; **5**; 240–247.
3. Daling JR, Madeleine MM, Johnson LG *et al*. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *Int. J. Cancer* 2005; **116**; 606–616.
4. Tsen HF, Morgenstern H, Mack T *et al*. Risk factors for penile cancer: results of a population-based case–control study in Los Angeles County (United States). *Cancer Causes Control* 2001; **12**; 267–277.
5. Hizli F, Berkmen F. Penile metastasis from other malignancies. A study of ten cases and review of the literature. *Urol. Int.* 2006; **76**; 118–121.
6. Chaux A, Amin M, Cubilla AL, Young RH. Metastatic tumors to the penis: a report of 17 cases and review of the literature. *Int. J. Surg. Pathol.* 2011; **19**; 597–606.
7. Eberth CJ. Krebsmetastasen des Corpus cavernosum penis. *Archiv f. Pathol. Anat.* 1870; **51**; 145–146.
8. Mearini L, Colella R, Zucchi A, Nunzi E, Porrozzi C, Porena M. A review of penile metastasis. *Oncol. Rev.* 2012; **6**; e10. Published 2012 Jun 14.
9. Cocci A, Hakenberg OW, Cai T *et al*. Prognosis of men with penile metastasis and malignant priapism: a systematic review. *Oncotarget* 2017; **9**; 2923–2930.
10. Cherian J, Rajan S, Thwaini A, Elmasry Y, Shah T, Puri R. Secondary penile tumours revisited. *Int. Semin. Surg. Oncol.* 2006; **3**; 33. Published 2006 Oct 11.
11. Zhang K, Da J, Yao HJ *et al*. Metastatic tumors of the penis: A report of 8 cases and review of the literature. *Medicine (Baltimore)* 2015; **94**; e132.
12. Giunchi F, Vasuri F, Valerio V *et al*. Unusual asymptomatic presentation of bladder cancer metastatic to the penis. *Pathol. Res. Pract.* 2017; **213**; 717–720.
13. Ellis CL, Epstein JI. Metastatic prostate adenocarcinoma to the penis: A series of 29 cases with predilection for ductal adenocarcinoma. *Am. J. Surg. Pathol.* 2015; **39**; 67–74.
14. Dutt N, Bates AW, Baithun SI. Secondary neoplasms of the male genital tract with different patterns of involvement in adults and children. *Histopathology* 2000; **37**; 323–331.
15. Morichetti D, Mazzucchelli R, Lopez-Beltran A *et al*. Secondary neoplasms of the urinary system and male genital organs. *BJU Int.* 2009; **104**; 770–776.
16. Grimm MO, Spiegelhalder P, Heep H, Gerharz CD, Röher HD, Ackermann R. Penile metastasis secondary to follicular thyroid carcinoma. *Scand. J. Urol. Nephrol.* 2004; **38**; 253–255.
17. Thyavihally YB, Tongaonkar HB, Gupta S, Gujral S. Primary seminal vesicle adenocarcinoma presenting as isolated metastasis to penis responding to chemotherapy and hormonal therapy. *Urology* 2007; **69**; 778.e1–778.e7783.
18. Pai A, Sonawane S, Purandare NC *et al*. Penile metastasis from esophageal squamous carcinoma after curative resection. *Ann. Thorac. Cardiovasc. Surg.* 2008; **14**; 238–241.
19. Masson-Lecomte A, Rocher L, Ferlicot S, Benoît G, Droupy S. High-flow priapism due to a malignant glomus tumor (glomangiosarcoma) of the corpus cavernosum. *J. Sex. Med.* 2011; **8**; 3518–3522.
20. Gerber R, Madersbacher S, Fleischmann A, Danuser H, Studer UE. Seltene seminommetastase im Corpus spongiosum und der urethra [rare seminoma metastasis to the corpus spongiosum and urethra]. *Urologe A.* 2003; **42**; 1491–1492.
21. Cimadamore A, Scarpelli M, Cheng L, Lopez-Beltran A, Montironi R. Extramammary Paget disease of the penis closely mimicking the penile analogue of stratified mucin-producing intraepithelial lesion. *Minerva Urol. Nefrol.* 2019; **71**; 189–190.
22. Keoghane SR, Sullivan ME, Miller MA. The aetiology, pathogenesis and management of priapism. *BJU Int.* 2002; **90**; 149–154.
23. Peacock AH. Malignant priapism due to secondary carcinoma in the corpora cavernosum. *Northwest Med.* 1938; **37**; 143–145.
24. Lin YH, Kim JJ, Stein NB, Khera M. Malignant priapism secondary to metastatic prostate cancer: a case report and review of literature. *Rev. Urol.* 2011; **13**; 90–94.
25. Skoog L, Collins BT, Tani E, Ramos RR. Fine needle aspiration cytology of penile tumors. *Acta Cytol.* 1998; **42**; 1336–1340.
26. Tsanou E, Sintou-Mantela E, Pappa L, Grammeniatis E, Malamou-Mitsi V. Fine-needle aspiration of secondary malignancies of the penis: a report of three cases. *Diagn. Cytopathol.* 2003; **29**; 229–232.