

ORIGINAL PAPER

Metastatic cancer to the penis: A multi-institutional comprehensive analysis of 31 patients

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Summary

Introduction: The metastatic spread of cancer to the penis is a very rare clinical entity generally associated with disseminated disease and poor prognosis. The aim of this paper was to show the outcomes of a series of patients treated for metastatic cancer to the penis and enhance the understanding and the management of penile metastasis in order to improve patients' care and outcomes.

Methods: We retrospectively analyzed the medical records of 31 patients diagnosed with metastatic cancer to the penis and treated at eight Ligurian urological departments between January 2014 and January 2024. Clinical characteristics, physical examination findings, diagnostic evaluations, treatment options and follow-up data were assessed.

Results: 27 (87%) patients had a prior history of malignancy with a metachronous metastasis. The most common primary site of malignancy was the genitourinary tract (71.1%) followed by the gastrointestinal tract (16.1%). The time interval from the diagnosis of the primary tumour to the detection of the penile metastasis was 36.0 months. The penile metastasis generally appeared with a mass (54.8%) and pain (29%), more rarely with priapism (6.5%), oedema (6.5%) and hematuria/urinary disorders (3.2%). The metastatic lesion required a total penectomy in 17 (54.8%) patients and a partial penectomy in 8 patients (25.8%). At a follow-up of 15.9 (1-75) months, 4 (18.2%) patients were still alive with disease.

Conclusions: Our data confirmed penile metastasis as a rare entity usually associated with clinical symptoms involving the penis in the context of a known primary malignancy, mainly from the neighboring pelvic organs, with a poor prognosis. The majority of our patients required a total penectomy with a negative impact on their quality of life. These aspects highlighted the importance of a penile examination and an early diagnosis of a penile metastasis during the follow-up schedule of many patients with a history of previous oncologic disease.

KEY WORDS: Penis; Penis cancer; Neoplasm metastasis; Metachronous neoplasm; Synchronous neoplasm.

INTRODUCTION

The metastatic spread to the penis from distant primary sites is a very rare phenomenon accounting for approximately 600 cases in the literature. While the management of primary tumors in the penis is rather well-defined, its involvement by metastatic lesions originating from other organs poses unique diagnostic and therapeutic dilemmas. In fact, the metastasis to the penis are generally associated with disseminated disease and poor prognosis (1-2). Understanding the different primary tumor origins, the pathogenetic mechanisms and the clinical implications of penile metastasis is necessary for healthcare professionals involved in the management and treatment of these patients.

More frequently, penile metastasis has been associated with primary tumors originating from urogenital cancers (69%) (2). However, metastasis from more unusual primary sites have been reported such as gastrointestinal tract (19%), kidney, lung and skin (2-6).

The aim of this paper was to show the clinical and the oncologic data of a multi institutional series of 31 patients affected by penile metastatic cancer in order to enhance the knowledge and the management of this condition and improve patients' care and outcomes.

MATERIALS AND METHODS

Patient population

We retrospectively analyzed electronic medical records of 31 consecutive patients diagnosed with metastatic cancer to the penis and treated at eight Ligurian urological departments between January 2014 and January 2024.

Clinical characteristics, including age, prior history of malignancy, metastasis at other sites, interval time between primary tumor and metastasis, presenting symptoms and physical examination findings were analyzed.

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Diagnostic evaluations, such as imaging studies and histopathological examinations, were assessed to confirm the presence of metastatic disease and determine the primary tumor origin. The pathology reports were carried out by individual dedicated pathologists.

Details regarding the management of penile metastasis were collected and analyzed. Treatment options included surgical and non-surgical interventions (lesion excision, partial or total penectomy, radiotherapy), systemic therapies (chemotherapy, targeted therapy, immunotherapy), and palliative interventions (pain management, supportive care). Patient follow-up data, including disease progression, response to treatment, and survival outcomes, were documented.

Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patient series. Continuous variables were expressed as means. Categorical variables were presented as frequencies and percentages. The descriptive statistical analysis was performed using R software environment for statistical computing and graphics (version 4.1.2).

RESULTS

Table 1 showed the demographics, oncological and clinical data of the patients.

Thirty-one patients with metastatic cancer to the penis were included in the study. The mean age at diagnosis was 72.3 years (range 21-83 years).

As regards the oncological history, twenty-seven (87%) patients had a known prior malignancy with a metachro-

Table 2.

Primary sites of metastatic solid tumors to the penis (n = 31).

N° of pts (%)	31
Bladder	15 (48.5)
Colon/rectum	4 (12.9)
Kidney	2 (6.5)
Skin	3 (9.6)
Pancreas	1 (3.2)
Urethra	2 (6.5)
Prostate	3 (9.6)
Bone marrow	1 (3.2)

nous presentation of penile metastasis; in the remaining four (13%), the penile involvement was synchronous with the initial clinical manifestation of the disease and the diagnosis of the primary cancer was achieved during the follow-up. Among these four patients, two were affected by bladder cancer, one by colorectal adenocarcinoma and another one by pancreatic carcinoma. Concerning the primary sites of malignancy, the most common was the genitourinary tract (71.1%) followed by the gastrointestinal tract (16.1%). Other uncommon primary sites included skin (9.6%), and bone marrow (3.2%). In particular, within the genitourinary system, the most recurring primary organ was the bladder (48.5%), followed by the prostate (9.6%), the kidney (6.5%) and the urethra (6.5%). Within the gastrointestinal tract, the most recurring primary location was the colon/rectum (12.9%), followed by the pancreas (3.2%) (Table 2). Microscopic images of metastatic solid tumors to the penis from urothelial carcinoma, colorectal adenocarcinoma and cutaneous melanoma are represented in Figure 1-3, respectively.

Regarding the staging of the primary tumor at diagnosis, it was pT3 and pT4 in twenty-one (67.7%) and ten (32.3%) patients respectively. Nodal involvement was assessed in twenty-three (74.1%) patients. Metastasis at other sites of primary cancer were assessed in six (19.3%) patients. Seventeen (54.8%) patients underwent an adjuvant therapy after the treatment of the primary cancer (hormonal therapy, radiotherapy and/or chemotherapy). The mean time interval from the diagnosis of the primary tumour to the detection of the penile metastasis was 36.0 months (range 0-240 months). In particular, the twenty-seven metachronous metastatic lesions developed within the first, third, fifth and tenth year since the initial diagnosis in seven (22,6%), ten (32.3%), four (12.9%), and three (9.6%) patients, respectively, and over the tenth year in the remaining three (9.6%) patients (Table 3).

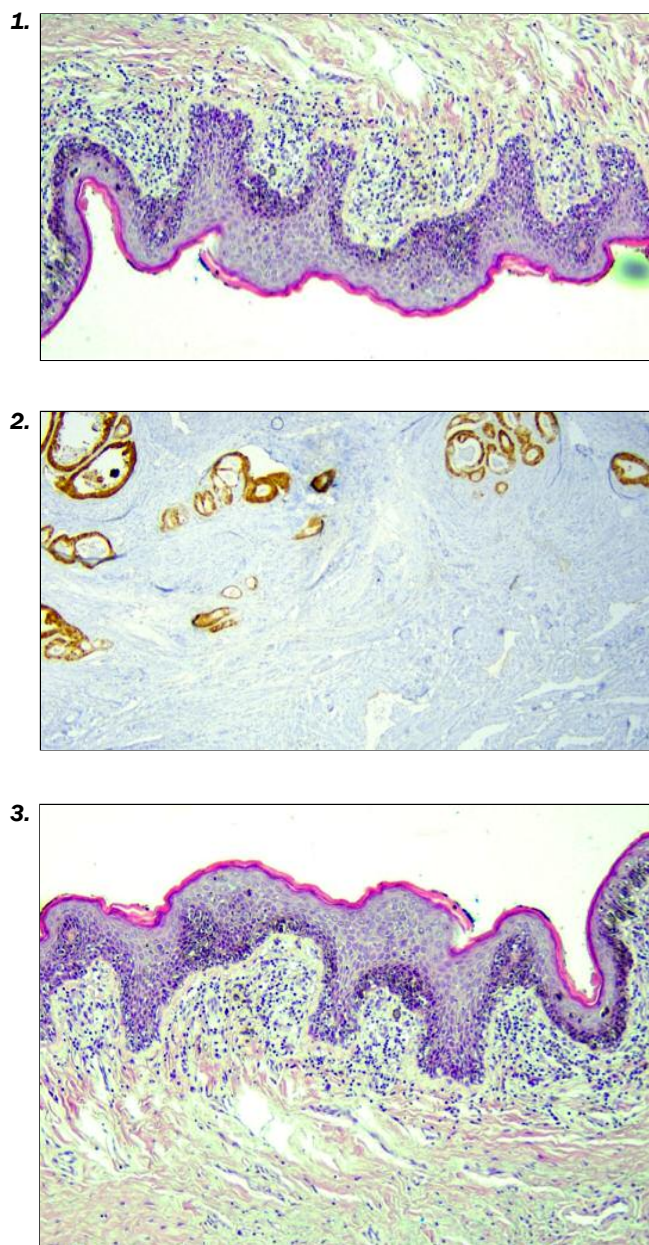
As concerns the clinical presentation of the penile metastasis, seventeen (54.8%) patients showed a bothersome mass or nodule. In particular this lesion was localized into the corpus cavernosum in twelve (70.5%) patients while in the glans in five (29.5%) patients. Furthermore, the penile lesions produced pain in nine (29%) patients, priapism in two (6.5%) patients, oedema in two (6.5%) patients and hematuria/urinary disorders in one (3.2%) patient. Regarding sexual activity, seven (22.5%) patients reported sexual intercourses, often occasionally, and rarely with the help of phosphodiesterase inhibitors.

Table 1.
Demographics, oncological and clinical characteristics of the patients.

N° of pts	31
Age (ys)	72.3 (21-83)
Previous history of cancer (n %)	
Yes	27 (87%)
No	4 (13%)
Staging of primary cancer (n %)	
pT3	21 (67.7%)
pT4	10 (32.3%)
Nodal involvement of primary cancer (n %)	
Yes	23 (74.1%)
No	8 (25.9%)
Metastasis at other sites of primary cancer (n %)	
Yes	6 (19.3%)
No	26 (80.7%)
Adjuvant therapy after primary cancer treatment (n %)	
Yes	17 (54.8%)
No	14 (45.2)
Interval time between primary tumor and metastasis (months)	36.0 (0-240)
Clinical manifestation of disease (n %)	
Mass/Nodule	17 (54.8%)
Pain	9 (29%)
Priapism	2 (6.5%)
Edema	2 (6.5%)
Hematuria/Urinary disorders	1 (3.2%)

Figure 1-3.

Microscopic images of metastatic solid tumors to the penis from urothelial carcinoma, colorectal adenocarcinoma and cutaneous melanoma.

**Table 3.**

Time interval between the primary tumor and penile metastasis (n = 31).

Months	n (%)
0 (Synchronous)	4 (12.9%)
1-12	7 (22.6%)
13-36	10 (32.4%)
37-60	4 (12.9%)
61-120	3 (9.6%)
> 120	3 (9.6%)

The metastatic lesion required a penectomy in the majority of the patients. In particular, total penectomy was performed in seventeen (54.8%) patients and a partial penectomy (nodule excision or glandulectomy) in eight patients (25.8%) followed by local radiotherapy in four of them. Among the remaining six patients, the diagnosis was performed with an excisional biopsy and not followed by any treatment procedure due to the poor patients' clinical conditions.

Follow-up data were available for twenty-two (70.9%) patients. Among these, at a mean follow-up of 15.9 (1-75) months, fifteen (68.2%) patients died of disease, four (18.2%) patients were alive with disease, three (13.6%) patients died for other causes.

DISCUSSION

The aim of this paper was to show the clinical and oncologic data of a multi institutional series of 31 patients affected by penile metastatic cancer in order to enhance the knowledge and the management of this condition and improve patients' care and outcomes. The metastatic spread of cancer to the penis is a very rare clinical entity with about 600 cases reported to date worldwide (1, 7-8). This aspect has been recently confirmed in the largest paper available in literature on this topic by *Nova-Camacho et al.* who described the data of 108 patients collected at twenty-two pathology departments from eight countries on three continents (8). The relatively small number of patients collected in our study resulted substantially in line with the outcomes reported by these authors. Actually, our data look rather more remarkable considering that they referred to only an Italian regional experience.

As regards the oncologic aspects, penile metastases are commonly identified in patients with known malignancies and an advanced disease (7-11). Accordingly, 87% of the patients of our series showed a metachronous metastasis, whereas the penile metastasis occurred synchronously with the primary tumour only in the remaining 13% of patients. Concerning these primary tumors, although we assessed different forms in terms of origins and histopathological characteristics, as expected, they were high stage primary cancers with nodal and metastatic involvement at diagnosis respectively in 74.1% and 19.3% respectively, which often required an extended surgery followed by an adjuvant treatment. Based on these aspects, also in our experience the penile metastasis generally occurred in a setting of advanced metastatic diseases.

Regarding the physiopathology of penile metastasis, the discrepancy between the relative blood supply and the rarity of the penis as site of secondary malignancy has been already reported. In particular, the retrograde venous route is thought to be the main way by which tumor cells from pelvic organs (prostate, urinary bladder, rectosigmoid) reach the corpus cavernosa and the glans, as the dorsal venous system of the penis has communication with the venous plexus system of the pelvis. Similarly, the retrograde lymphatic route seems to be the way by which tumor cells reach the penile skin via lymphatics that drain the pelvic organs, passing through the iliac and inguinal nodes (7-8). Less commonly, arterial spread, direct extension or iatrogenic spread by instru-

ments, could explain metastasis from closer or distant organs as the kidneys, the hematologic system, the liver and the lungs or other organs (12-16). According to the seed/soil hypothesis and to the fact that the site of metastasis is determined not only by the characteristics of the neoplastic cells but also by the microenvironment of the host tissue, the penis probably does not provide the perfect environment (soil) for neoplastic seeding.

Furthermore, the rich communications between arterial inflow and venous outflow could explain the difficulty in cell seeding in normal conditions. However, when the outflow is impaired by venous or lymphatic occlusions, such as in the presence of a tumor in the neighboring genito-urinary organs or in massive pelvic disease, the process of seeding could be facilitated (7). Our data showed that 80% of the metastatic lesions originate from the neighboring genito-urinary and pelvic organs, mainly bladder, prostate and rectum-sigmoid confirming the more validated hypothesis that the venous or lymphatic flows could be the routes by which tumor cells reach the penis from these organs. Regarding the interval time between the primary tumor and the development of metachronous metastasis, it was 3 years in our series. This period of time looks rather surprisingly and longer than expected considering the high risk of the primary tumors. However, a similar time interval between the primary diagnosis and the occurrence of the penile metastasis has been already reported in literature and probably explained by the effect of the adjuvant treatments on patients' surveillance (8).

As concerns the clinical presentation of the metastasis, our data confirmed that the majority of the patients (84%) showed symptoms associated with penile nodules and pain. This aspect highlighted the importance that physicians become worried of an eventual penile metastasis in case of a known history of primary tumors and clinical symptoms involving the penis, especially following previous pelvic tumors diagnosed even some years before considering also the documented patients' tendency to delay the presentation and diagnosis of penile lesions. In case of penile pain, particular attention should be paid at the differential diagnosis between penile metastasis and Peyronie's disease, especially when the pain is reported also in flaccidity (17).

Regarding the management of penile metastasis, there is no consensus in literature regarding the best treatment to choose. This aspect is likely due to insufficient data available and the worse prognosis for these patients. In particular, the decision between radical or partial penectomy and/or radiation therapy is balanced considering the primary tumor, the size, location and number of metastatic lesions, patient's age, performance status and motivation [1, 7-10, 18-20]. In our experience, the majority of patients (80%) required a penectomy which was mainly a total penectomy. In fact, a partial penectomy (nodule excision or glandulectomy) was feasible only in 25.8% of patients. Although the mean age of our study population was rather old (72 years) and the prognosis of these patients rather poor, we can neglect that 22.5% of them still reported a sexual activity and that an earlier diagnosis and treatment of the metastasis could allow a less invasive surgery with a less impact on function (sexual, urinary or sensory), genital appearance, quality of life and

psychological well-being, especially in younger patients. In fact, negative impact on quality of life has been described in some studies following penile cancer surgery, variably correlated with aggressiveness of penile surgery. Furthermore, anxiety, depression, and reduced self-esteem have been reported in penile cancer survivors (20-22). These aspects highlight again the importance of a penile examination and an early diagnosis of penile metastasis during the follow-up schedule of many patients with a history of previous oncologic disease. Finally, in our experience 68.2% of patients died of disease and a very low cancer specific surveillance (18.2%) was assessed at 16 months follow-up. This is also in accordance with the previous data that show poor prognoses for these patients due to a disseminated disease and a poor general health which cause death generally within a year from the presentation (7-9).

The retrospective nature of this study may be subject to inherent limitations, such as missing data, incomplete documentation, and potential selection bias.

Additionally, the generalizability of the findings may be influenced by the specific characteristics of the patient population treated at different participating institutions.

CONCLUSIONS

Our data confirmed penile metastasis as a rare entity usually associated with clinical symptoms involving the penis in the context of a known primary malignancy, mainly from the neighboring genito-urinary and pelvic organs, with a poor prognosis. The majority of our patients required a

DECLARATIONS

Ethical approval: The authors declared that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Availability of data and material: All inquiries can be directed to the corresponding author.

Competing interests: The author has no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. All authors declared that all data and materials as well as software application or custom code support their published claims and comply with field standards.

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total penectomy with a negative impact on their quality of life. These aspects highlighted the importance of a penile examination and an early diagnosis of a penile metastasis during the follow-up schedule of many patients with a history of previous oncologic disease in order to allow more effective and less invasive management strategies for alleviating the symptoms, preserving the sexual function, and improving the overall quality of life.

Overall, our study on penile metastasis not only enhances our understanding of cancer systemic development and progression but also remarks the importance of a multidisciplinary collaboration among urologists, oncologists, radiologists, and pathologists. Continuous research and clinical investigations, should allow us to optimize diagnostic accuracy, improve treatment approaches, and enhance the overall care of the patients affected by this rare metastatic disease.

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