Case Report

Surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy of rectal adenocarcinoma with penile metastasis: a case report

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Background: Despite the rich proximity and vascularization to the pelvic organs, metastatic lesions to the penis are incredibly uncommon. Most primary tumors are genitourinary cancers, and rectal origins are rare. Only 56 cases of metastatic penile tumors have been reported since 1870. Several palliative or curative methods, such as chemotherapy, total penectomy, and radiotherapy, have been applied to treat this condition in previous cases; however, the patient prognosis is poor. Immunotherapy is a beneficial treatment approach for multiple cancers, and recent investigations have shown that it may be beneficial for patients with advanced penile cancer.

Case Description: Herein, we report the case of a 59-year-old Chinese man who had metastatic adenocarcinoma in the penile tissue 3 years after rectal cancer resection. The patient presented with penile pain and dysuria for 6 months when he was 54 years old, and Immunohistochemical staining showed that the origin was the rectum after total penectomy. The patient received surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy positively and still survived for a further 4 years and 6 months following penectomy despite the late metastasis of rectal cancer. There are two major changes and progress after penectomy, all of which have undergone surgical treatment during continuous treatment and follow-up, the patient completed right inguinal lymphadenectomy when his right regional nodes metastasis was found 23 months after penectomy. While the patient suffered from radiation injury after 47 months after penectomy, which led to radiation necrosis and hip soft tissue infection, and the patient tended to lay prone instead of lying on the back because of the hip pain. The patient ultimately died of multiple organ failure.

Conclusions: All of the previously reported cases of penile metastasis from rectal cancer since 1870 have been reviewed. Yet, the metastatic prognosis remains poor regardless of the treatment options, except for lesions where metastasis is only limited to the penis. We found that the patient may derive more benefit from strategic therapies including surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy.

Keywords: Metastatic rectal adenocarcinoma; penile metastasis; case report; prognosis; treatment

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Introduction

The penis is an uncommon site of metastatic colorectal adenocarcinoma (1). The first reported case of penile metastases from rectal adenocarcinoma was reported by Eberth in 1870 (2). Beatriz Nunes *et al.* reported a patient with a metastasis to the glans penis from a rectal adenocarcinoma underwent palliative treatment with radiotherapy and chemotherapy, remaining asymptomatic and disease-free at one year follow-up (3). Boubacar Efared *et al.* disclosed a patient with penile metastasis from rectal adenocarcinoma who accepted his adjuvant chemotherapy (XELOX regimen, oxaliplatin plus capecitabine) (4). A patient underwent palliative chemotherapy treatment and still alive 4 months after diagnosis of penile metastases (5). Lee *et al.* reported a patient with metastatic carcinoma from the rectal cancer and the patient was still alive after receiving palliative chemotherapy with modified FOLFOX-6 (mFOLFOX-6; oxaliplatin with 5-fluorouracil and folinic acid) plus bevacizumab (6). On average, penile metastasis from rectal adenocarcinoma can occur within 2 years after the diagnosis of the primary tumor (7).

Several palliative or curative methods have been applied in previous cases, such as chemotherapy, total penectomy, and radiotherapy; however, the patient prognosis remains poor. The knowledge gaps and limitations of prior study is low incidence of rectal adenocarcinoma with penile metastasis, inexperience of treatment and the lack of standard treatment guidelines. The clinical significance of this study is early detection, precise diagnosis, patient's positive psychology that we guided and comprehensive treatment including surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy.

We applied targeted therapy and immunotherapy in this case, and the prognosis was not poor after phallectomy. We also performed a literature search and found 56 previously reported cases of rectal cancer spreading to the penis (*Table 1*) and the table revealed the ages, interval of metastasis, treatment of rectal cancer, treatment of metastasis, other metastasis and prognosis of patients from different regions or countries. The prognosis of our patient is 54 months after being diagnosed with metastasis of penile cancer, and the patient benefited from the strategic treatment and improved the quality of life. We present the following article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-84/rc).

Highlight box

Key findings

- In addition to surgery, radiotherapy, and chemotherapy, strategic therapies including targeted therapy and immunotherapy may provide a more comprehensive and effective choice for the treatment of rectal cancer, especially for advanced rectal cancer.

What is known and what is new?

- What is known is that previous studies including local excision, partial or complete penectomy, external beam radiotherapy, brachytherapy and chemotherapy have been more palliative than curative. These studies have demonstrated a poor prognosis in advanced rectal cancer.
- What is new is that our patient insisted on positive treatment based on systemic therapy combined with immunotherapy and survived for up to 4 years and 6 months following penectomy, despite multiple rectal cancer metastases. Strategic therapies including surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy may contribute to improving the quality of life of patients and prolonging their survival.

What is the implication, and what should change now?

- Patients with advanced rectal cancer including penile metastasis may derive more benefit from comprehensive treatment.

Case presentation

Four years and six months ago, a 54-year-old Chinese man presented with penile pain and dysuria for 6 months, without a family history of rectal or penile cancers. The patient was hospitalized, and the physical examination showed multiple hard nodules of the penile shaft and glans with visible skin ulceration on the penile glans (*Figure 1*). The man died at the age of 59 years due to multiple organ failure. He had undergone abdominoperineal resection for adenocarcinoma of the rectum 7 years and 6 months previously, and the contrast-enhanced computed tomography (CT) scan showed that this case was consistent with the postoperative manifestations of rectal cancer. Given that the penile metastasis was solitary, we performed a total penectomy and paracentetic suprapubic cystostomy 4 years and 6 months prior.

Pathological biopsy revealed multiple metastatic adenocarcinoma tissues in the penis (*Figure 2*), and immunohistochemistry confirmed the hypothesis of rectal adenocarcinoma metastasis. Tumor cells were positive for CDX-2 (caudal type homeobox transcription factor 2), Villin, CK20 (cytokeratin20) and the Ki-67 index reached up to 50%; negative for TTF-1 (thyroid transcription factor1), and CK7 (cytokeratin7).

Table 1 All of the previously reported cases

Author, ref	Year	Age, years	Interval of metastasis, months	Treatment of rectal cancer	Treatment of MTS	Other metastatic sites	Prognosis
Our case	2022	59	54	APR	TP, PC, RT, cetuximab, right inguinal lymphadenectomy bevacizumab, sintilimab injection	Lymphonodus, bone, lung	54 m
Lee (6)	2020	74	9	Neoadjuvant CRT, APR	PC	None	4 m
Marghich (5)	2019	47	4	APR	PC	Bone, lung, lymphonodus	4 m
Ahmad (8)	2019	51	NA	NA	PC	NA	NA
Kuliavas (9)	2018	41	17	CTR, PP, RT	TP	Bladder	2 m
Efared (4)	2017	46	8	APR	TP	None	NA
Kozan (10)	2016	58	18	APR	TP	None	Follow-up
Nunes (3)	2015	66	15	RT	CRT, RT	None	Follow-up
Christodoulidou (11)	2015	70	24	Neoadjuvant CRT, LAR	TP	Lung	NA
Alzayed (12)	2015	70	26	Neoadjuvant CRT/RT, APR	NA	Lung	NA
Persec (7)	2014	43	24	LAR, neoadjuvant CRT	PP	NA	6 m
Hajianfar (13)	2014	78	24	LAR, neoadjuvant CRT	PP	NA	3 m
McGuinness (14)	2013	61	60	LAR	Circumcision, glansectomy	NA	NA
Dorsett (1)	2012	61	NA	CRT	Penectomy	Lung	4 m
Kimura (15)	2012	57	16	APR	Penectomy	NA	24 m, alive
Gbenou (16)	2011	79	24	LAR	Refused	NA	6 m
Seo (17)	2011	72	7	APR	CRT	Liver, bone	Death
Yildirim (18)	2010	78	36	Neoadjuvant CRT/RT, APR	CRT	Diffused	Poor
Küronya (19)	2009	65	54	LAR	CPT	None	NA
Park (20)	2009	43	24	APR	CPT	Lung, bone lymphonodus	NA
Chung (21)	2008	69	Meanwhile	NA	RT	Liver	6 m, alive
Ketata (22)	2007	59	312	APR	CPT	Lung	16 m, alive
Murhekar (23)	2007	78	24	APR	Refused	NA	4 m
Pellicé i Vilalta (24)	2006	NA	NA	NA	NA	NA	NA
Cherian (25)	2006	75	60	APR	PT	Lung	12 m
Cathomas (26)	2006	58	26	LAR	CRT	Liver, lung	Poor
Appu (27)	2006	65	24	APR	RT	None	12m
Yilmaz (28)	2004	71	24	LAR	NA	None	2 w, death
Lo (29)	2004	56	24	APR	NA	NA	NA
Tan (30)	2002	53	Meanwhile	APR	RT	NA	NA
Sukumar (31)	2001	75	2	APR, CTR	RT	NA	2 m

Table 1 (*continued*)

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Author, ref	Year	Age, years	Interval of metastasis, months	Treatment of rectal cancer	Treatment of MTS	Other metastatic sites	Prognosis
Al-Mashat (32)	2000	65	19	APR	No treatment	NA	5 m
Lange (33)	1997	42	NA	APR	Surgical treatment	NA	NA
Cuvillier (34)	1995	NA	29	APR	CRT	NA	15 m
Comandone (35)	1992	NA	NA	NA	PT	NA	NA
Doré (36)	1989	58	NA	NA	NA	NA	NA
Mukamel (37)	1987	58	2	NA	No treatment	NA	5 m
Khubchandani (38)	1986	71	48	APR	RT	NA	9 m
Honda (39)	1985	69	10	CTR, RT	Surgical treatment	NA	NA
Honda (39)	1985	60	24	APR	NA	NA	NA
Okumura (40)	1984	45	22	Resection	NA	NA	NA
Kakehi (41)	1984	72	NA	NA	NA	NA	NA
Kakehi (41)	1984	42	NA	NA	NA	NA	NA
Kakehi (41)	1984	66	NA	NA	NA	NA	NA
Zanetti (42)	1983	NA	NA	NA	NA	NA	NA
Kumar (43)	1980	70	4	APR	Fluorouracil and irradiation	Lung	5 d
Rees (44)	1975	41	33	APR	Penectomy	NA	8 m, alive
Rees (44)	1975	71	24	APR	CRT	Lymphonodus	Good
Sakkas (45)	1974	48	NA	CRT	CRT	NA	6 m
Bachrach (46)	1973	59	NA	NA	NA	liver	2 w
Poser (47)	1972	59	NA	APR	NA	NA	2 m, alive
Tagart (48)	1967	75	108	APR	TP	None	5 y
Ongenae (49)	1967	NA	NA	NA	NA	NA	NA
Oehlschlaegel (50)	1966	NA	NA	NA	NA	NA	NA
Cattell (51)	1951	30	29	APR	Resection	NA	NA
Eberth (2)	1870	40	NA	NA	NA	NA	NA

MTS, metastasis; APR, abdominoperineal resection; LAR, low anterior resection; TP, total penectomy; PP, partial penectomy; PC, palliative chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; LAR, low anterior resection; CTR, chemotherapy; NA, not available; d, days; m, months; y, years.

The patient received chemotherapy and radiotherapy after surgery, but metastasis to the right regional nodes was found 23 months after penectomy. Genetic testing was performed after the patient completed right inguinal lymphadenectomy. The patient accepted therapy involving surgery, palliative chemotherapy, radiotherapy, right inguinal lymphadenectomy, Cetuximab, Bevacizumab, and Sintilimab injection.

Six cycles of chemotherapy were administered with Iritecan 320 mg d1 and Tessio 60 mg d1–d14 53 months previously, and radiotherapy with DT 59.6 Gy/32 f was administered 47 months previously. Right inguinal lymph node metastasis was found 31 months ago, and right inguinal lymphadenectomy was performed. Six cycles of

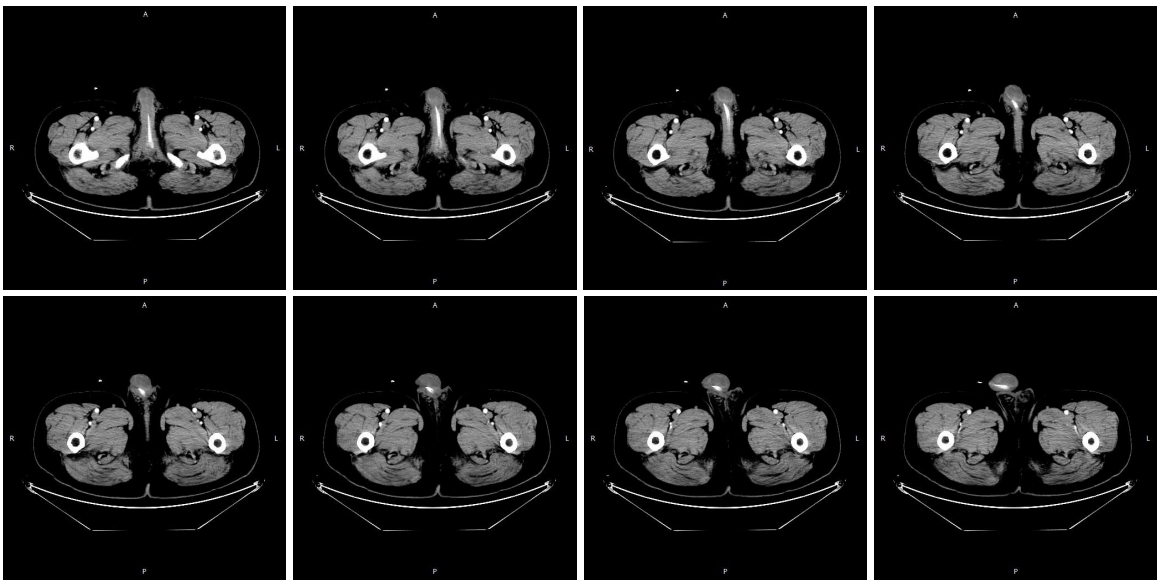

Figure 1 Computed tomography, penile neoplasms and anterior urethral stricture.

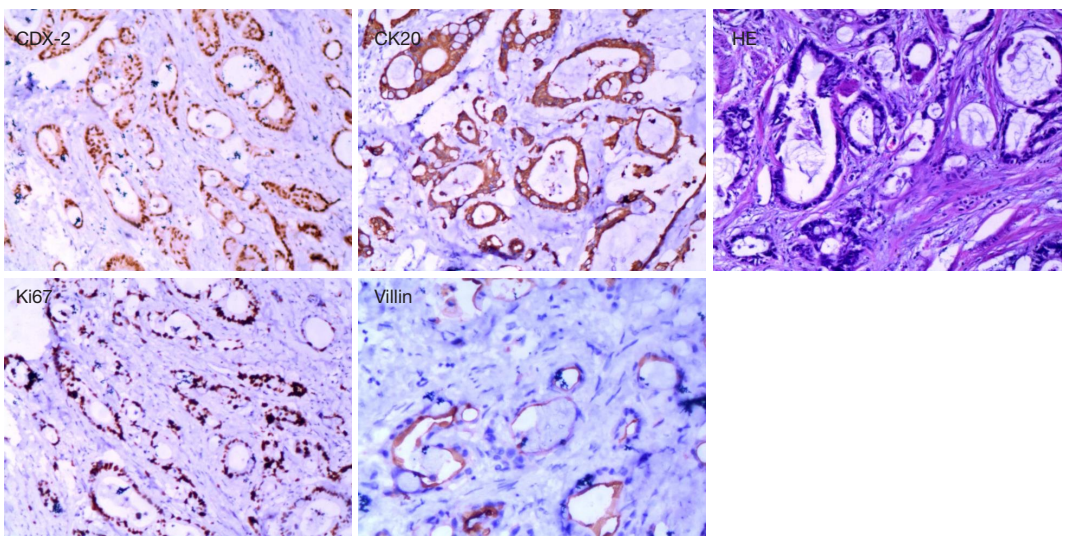

Figure 2 Immunohistochemistry, positive for CDX-2 (×100), Villin (×200) and CK20 (×100), Ki-67index 50% (×100), HE (hematoxylin-eosin staining, ×100). HE revealed the rectal adenocarcinoma cells.

therapy with Cetuximab 800 mg d1, Iritecan 320 mg d2 and continuously-pumped Fluorouracil 3.5 g was used 29 months previously. Pelvic bone and lymph node metastases were found 24 months ago, radiotherapy with DT 50 Gy/25 f was administered 20 months previously, and the patient was then treated with cetuximab.

The PET-CT found multiple bone (right femur, right sacroiliac joint, ischia, pubis) metastases, and the gene test results showed that Bevacizumab was sensitive 15 months previously. The patient also felt severe low back pain and need painkillers. Bevacizumab 400 mg d0, irinotecan 300 mg d1, and fluorouracil 0.5 g d2–6 were administered 14 months previously. Cindilimab 200 mg was also used 13 months previously. Meanwhile, the pelvic bone and lymph node metastases were treated by radiotherapy with DT 50 Gy/25 f 12 months previously. Moreover, the lymph

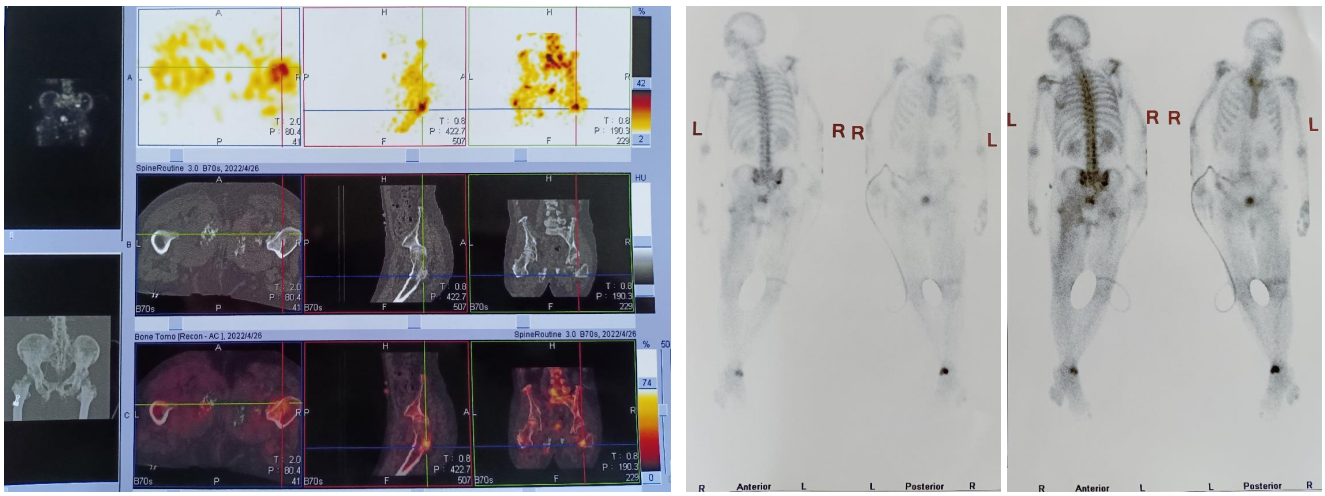

Figure 3 Bone metastasis (right femur, right sacroiliac joint, ischia, pubis), the patient tends to lie prone. SPECT/CT, single-photo emission computed tomography/computer tomography.

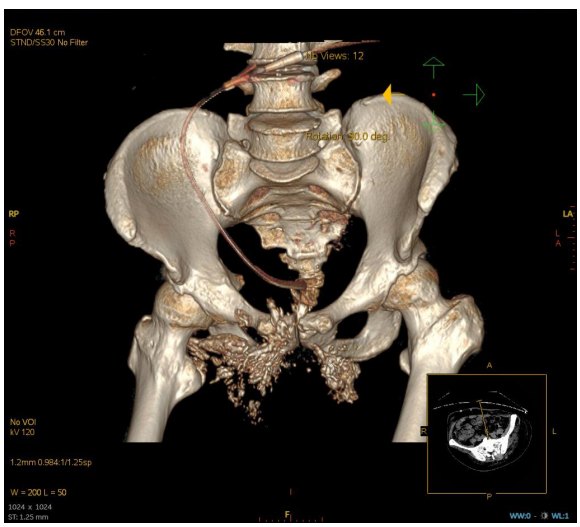

Figure 4 CTU, bone metastasis and osteonecrosis. CTU, computed tomography urography.

nodes, soft tissue, and femur tumor metastases were treated by radiotherapy with DT 60 Gy/30 f 12 months previously. One cycle of Cindilimab, Bevacizumab, and Capecitabine was applied 10 months prior.

Radiation necrosis, hip soft tissue infection, and pyogenic buttocks were found 7 months previously, and the patient tended to lay prone and could not lie on his back (*Figure 3*). We disinfect with iodophor (the available iodine content, 4.4 to 5.0 g/L) twice a day if there are cutaneous manifestations of metastatic disease to the penis. Chest-enhanced CT showed lung metastasis and Cindilimab was administered 4 months previously. Incision and drainage of hip and left thigh lateral root abscesses were also performed 4 months previously (*Figures 4-6*). We added the *Figure 6* as a timeline figure to arrange the events and interventions in chronological order with dates.

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family member for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Herein, we reported the outcomes of our experience treating a patient with rectal adenocarcinoma metastasis to the penis and found that the patient, who was treated with active treatments, had positive control outcomes. In addition, we observed that the patient may have derived more benefits in terms of disease control from strategic therapies.

Colorectal cancer has become common worldwide and is a frequent cause of cancer-related death (52). Surgical treatment is an effective therapy for rectal tumors. It is

reported that lymphadenectomy with venation is preferred for radical resection in some patients (53). Rectal cancer patients have more symptoms and decreased performance status in the presence of advanced disease, and the quality of life of these patients can also be impacted (54). Penile cancer is a rare malignancy, and patients with this condition tend to delay seeking medical attention, which may lead to poor outcomes (55). Recent findings in penile cancer have motivated several trials evaluating new modalities of systemic treatments, especially immunotherapy (56). Sintilimab is a recombinant humanized lgG4 anti-PD-1 antibody, with affinity to human programmed cell death protein 1 (PD-1). Lv *et al.* (57) reported that a patient of recurrent and metastatic penile squamous cell carcinoma obtained progression-free survival with continuous sintilimab. Immune-based treatments coupled with systemic therapy may offer benefits to patients with advanced penile cancer (58).

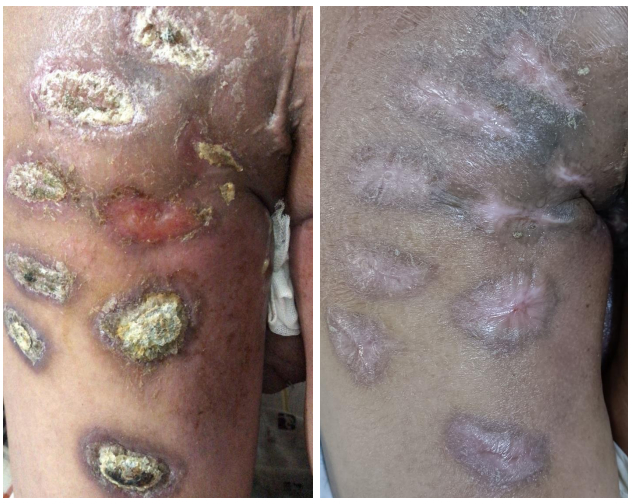

Figure 5 Left: before treatment; right: after treatment.

Tumor response was investigator assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) (59) or immune Response Evaluation Criteria in Solid Tumors (iRECIST) (60). Cancers develop in complex tissue environments, depending upon for sustained growth, invasion and metastasis. Cancers develop in complex tissue environments, depending upon for sustained growth, invasion and metastasis. The establishment of an antitumor immune response and memory can eliminate tumor cells, prevent recurrence in the primary region and inhibit metastasis to distant sites (61). Cytokine therapy (62), cancer vaccines (63), immune checkpoint blockade (ICB) (64) and adoptive cell transfer (ACT) therapy (65) focus on boosting immune response and immune cell activities in the tumor microenvironment (TME), and the ICB function can inhibit local tumor progression and systemic metastasis.

Immunotherapies have led to substantial changes in cancer treatment and been a popular topic in cancer research. Mismatch repair deficiency or microsatellite instability-high is significantly associated with long-term immunotherapy-related responses and better prognosis in colorectal and noncolorectal malignancies treated with immune checkpoint inhibitors (66). The efficacy of PD-1/PD-L1 inhibitors varies among different classic driver oncogene mutations (67), KRAS-mutant patients appeared to respond better to anti-PD-1/PD-L1 immunotherapy, while patients with EGFR mutant disease may obtain benefits from immunotherapies, but the detailed mechanistic explanation needs further research. As a specific RNA adaptor, THUMPD1 (68) is significantly associated with immune cell infiltration, tumor mutational burden (TMB), microsatellite instability (MSI), immune checkpoints and neoantigen. Patients with higher THUMPD1 expression exhibited a better prognosis in kidney renal clear cell carcinoma (KIRC) and rectum adenocarcinoma (READ), while worse prognosis in liver hepatocellular carcinoma

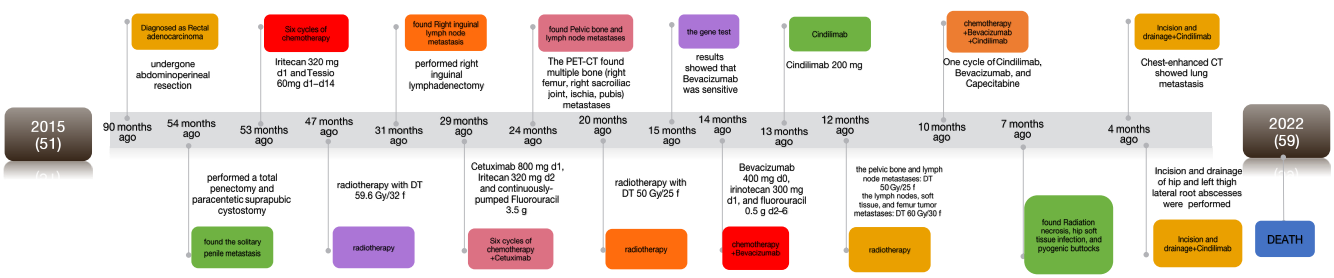

Figure 6 A timeline figure. DT, dose total; Gy, gray; PET-CT, positron emission tomography-computed tomography; CT, computed tomography.

(LIHC) patients, so THUMPD1 may be a novel predictor to evaluate cancer prognosis and immune therapy efficacy in diverse cancer types. More predictors are required further exploration and research.

Penile metastases from rectal cancer are extremely rare. The most common primary malignancies with penis metastases are urogenital cancers (69%); gastrointestinal origin accounts for 19%, with the sigmoid colon and rectum accounting for 12% of all such cases (69). Although rectal adenocarcinoma is a common malignant tumor of the digestive system, which usually metastasizes to local lymph nodes, the lung, the liver, and bone, penile metastasis from rectal cancer is rare, and these lesions can occur without any liver or lung involvement (16). Perineal pain, induration, urethral obstruction, priapism, and hematuria are the most common associated symptoms. In 40% of patients, priapism is considered a prominent feature. Metastases can present as plaques, wart-like nodules, ulceration, erythema, or induration of the penis (5). The mass ordinarily progresses to involve the corpora cavernosa with extension into the neighboring perineal subcutaneous tissue, the corpus spongiosum, and bulb (6). Although pain is not the patient's initial symptom, it is often the most prominent symptom in the later stage. Given that penile metastasis from rectal adenocarcinoma can commonly occur within 2 years after the diagnosis of a primary tumor, combining the history and other clinical manifestations would help to suspect the disease early. To confirm the diagnosis of penile metastasis, immunohistochemical staining is beneficial for discriminating the origin of the cancer. Primary adenocarcinoma of the colon and metastatic lesions can be strongly negative for CK 7 and positive for CK 20 (17). The patient received chemotherapy for metastatic disease until disease progression and unacceptable toxicity and he died with progressive disease, and tissue tumor markers, such as AFP, CEA, and HCG can be used for differential diagnosis (18).

Despite its rich and interconnected vasculature and its proximity to the genitourinary system, in which the prostate and bladder are both popular sites for tumor metastasis, metastatic tumors from colorectal cancer rarely involve the penis. There have been many hypotheses regarding penile metastasis from rectal cancer. Yet, the retrograde venous route is the most commonly accepted route of metastasis since the dorsal venous system of the penis can communicate with the venous plexus system of the pelvis. Through this mechanism, the retrograde lymphatic course may be how tumor cells from pelvic organs (rectosigmoid, prostate, urinary bladder) reach the corpus cavernosal and the glans via the lymphatics and iliac inguinal nodes. Other less common ways include direct extension, arterial spread, or the iatrogenic spread by instruments, as well as secondary penile root tumors from adjacent pelvic organs (4). Since the left and right inguinal lymph nodes are fibrous adipose tissue and no cancer was observed in our case, we speculated that our case was via the retrograde venous metastasis route.

Various therapies have been attempted for the treatment of penile metastases, such as total penectomy, radiotherapy, and chemotherapy. However, these approaches have been more palliative than curative. Overall survival normally varies from 7 months to 2 years when the tumor spreads diffusely. Long-term survival (9 years) has been observed following aggressive surgery (penile amputation), with the best patient outcomes occurring in cases of penile metastasis being the only evident region of recurrence. More clinical treatment research exploration, multi-center study and public network database to achieve global sharing of cancer data may bring greater clinical benefits to the patients. More comprehensive analysis of multiple markers may also provide the appropriate strategy in the future.

The choice of treatment of our patient have a palliative intention, but these therapeutic options may lead to superior treatment outcomes especially when considering the patient's positive attitude. We speculate that comprehensive treatment including surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy and helping patients have a positive and optimistic attitude may contribute to improve the clinical management of similar cases.

Conclusions

The metastatic prognosis remains poor regardless of the treatment options, except for lesions where metastasis is only limited to the penis. The metastatic carcinoma of the penis in our case was solitary, and surgical penectomy seemed to improve the prognosis, which was not poor. We found that the patient may derive more benefit from strategic therapies and positive attitude. Thus, the similar patients may benefit from multiple aggressive therapies and survive longer.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-84/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-84/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-84/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family member for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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