



Urothelial carcinoma with trophoblastic differentiation: case report and review of literature

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Abstract

Urothelial carcinoma with trophoblastic differentiation (UCTD) is a rare histological variant of urothelial carcinoma characterized by the presence of trophoblastic elements and expression of β -human chorionic gonadotropin (β -hCG). Published evidence is limited, and the clinical behavior of this variant remains incompletely understood. The objective of this study is to review the available literature regarding the incidence, clinicopathological characteristics, treatment modalities, recurrence patterns, survival outcomes, and prognostic implications and to present the case of a patient with UCTD.

A 66-year-old male patient presented in February 2025 with a 2-month history of progressive left inguinal swelling and recurrent left hydrocele. Past medical history revealed: radical cystectomy with ileal neobladder, pelvic lymphadenectomy (for bladder pT2G3 recurrent BCG resistant bladder tumor) performed on the 28th of June 2018. Full body contrast CT scan had been performed on the 24th of December 2024 and revealed a left inguinal adenopathy conglomerate 9.93 cm in length, with the largest lymph node measuring 2.5 cm, bilateral peritesticular fluid collections (hydrocele) with no evidence of local tumor recurrence in the neobladder or prostate bed and a supradiaphragmatic, calcified pleural mass (3.4×1.8 cm).

Scrotal ultrasound revealed: large bilateral hydrocele, left epididymal and upper testicular pole tumor (~2 cm in size) with increased Doppler vascularity and a large left inguinal adenopathy conglomerate (~10 cm in size) with increased Doppler vascularity. Testicular cancer serum markers were performed and a serum β -hCG of 5893 mIU/ml, was found. Ultrasonographical assessment and positive testicular cancer biomarkers prompted us to suspect a testicular tumor with inguinal lymph node metastases. Patient was referred for surgery. Left inguinal radical orchidectomy was performed along with left inguinal lymphadenectomy. Histopathological examination of the testicle revealed testicular and epididymal inflammation. Lymph node examination revealed urothelial carcinoma with squamous and trophoblastic differentiation, PDL1(22C3) positive, CK7 positive, GATA3 positive, CK20 positive, p16 negative and beta HCG positive on 10% of cells. Patient was started on platinum-based chemotherapy with rapid disease progression and died of metastatic complications approximately 11 months after the initial recurrence signs were visible on the CT scan.

Conclusions. UCTD is a rare and aggressive variant of urothelial carcinoma associated with unfavorable oncological outcomes. Available evidence supports aggressive treatment and prolonged follow-up. To our knowledge, this may represent one of the few reported, very late recurrences after radical cystectomy.

Keywords: urothelial cancer, trophoblastic differentiation, recurrence, β -human chorionic gonadotropin

Case Report

We present the case of 66-year-old male patient with a past medical history of: radical cystectomy with ileal neobladder, pelvic lymphadenectomy (for bladder pT2G3 recurrent BCG resistant bladder tumor) in June 2018 and left hydrocele surgery performed in March 2024. The patient presented to our department on the 22nd of February 2025 with a 2-month history of progressive left inguinal swelling (Fig.1) and recurrent left hydrocele. Scrotal ultrasound revealed: large bilateral hydrocele,

left epididymal and upper testicular pole tumor (~2 cm in size) with increased Doppler vascularity and a large left inguinal adenopathy conglomerate (~10 cm in size) with increased Doppler vascularity (Fig.2). Full body contrast CT scan performed in December 2024 revealed: a lobulated pleural mass with calcifications (3.4×1.8 cm in size); a 9.93 cm left inguinal adenopathy conglomerate; bilateral peritesticular fluid collections (hydrocele) (Fig.3, Fig.4); with no evidence of local tumor recurrence in the neobladder or prostate bed.



Fig. 1. Left inguinal and testicular swelling.

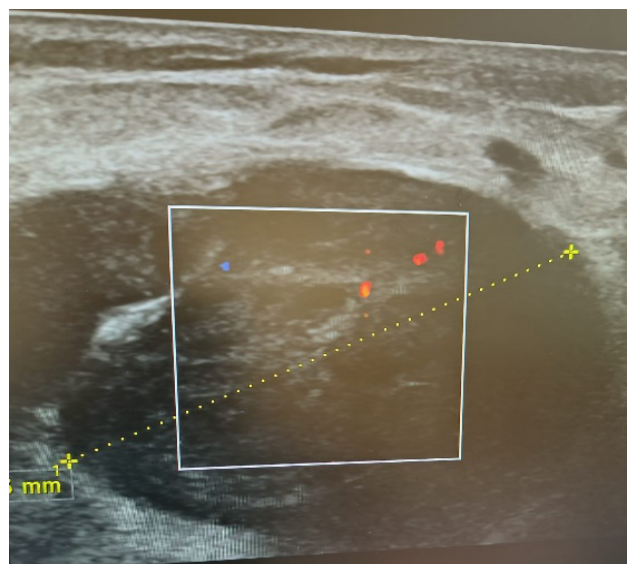


Fig. 2. Ultrasound aspect of inguinal node.



Fig. 3. CT aspect of testicles.

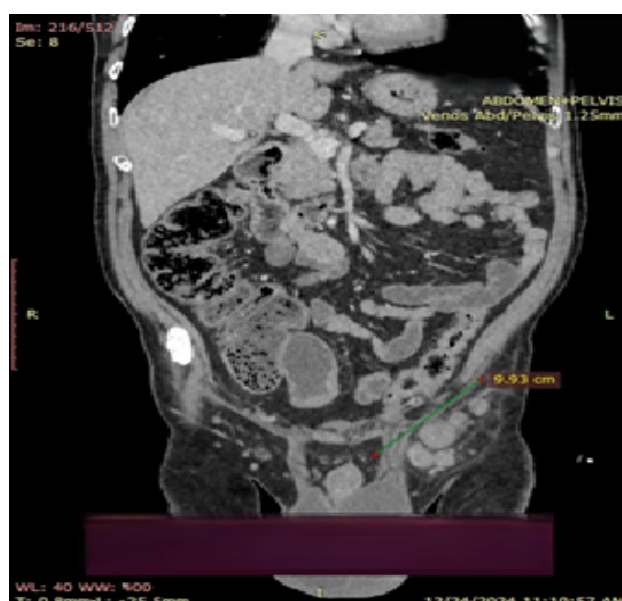


Fig. 4. Left inguinal lymph nodes.

Testicular cancer serum markers were performed and a serum β -hCG of 5893 mIU/ml, was found. Other modified laboratory tests were WBC- $11.90 \times 10^9/L$; C reactive protein 114 mg/dl; mild anemia Hgb-10.9 g/dl. Ultrasonographical assessment and positive testicular cancer biomarkers prompted us to suspect a testicular tumor with inguinal lymph node metastases. Left inguinal radical orchiectomy was performed along with left inguinal lymphadenectomy. Postoperative course was uneventful, managed with Ceftriaxone + Gentamicin, analgesics, and LMWH prophylaxis (enoxaparin 40mg/day). Patient was discharged on the 3rd postoperative day. Histopathological examination of the testicle revealed testicular and epididymal inflammation. Lymph node examination (Fig. 5, Fig. 6) revealed urothelial carcinoma with squamous and trophoblastic differentiation, PDL1 (22C3) positive, CK7 positive, GATA3 positive, CK20 positive, p16 negative and beta HCG positive on 10% of cells. Patient was referred to oncology department for reevaluation and adjuvant chemotherapy.

On the 23rd of May 2025 the patient underwent abdomen and pelvis contrast enhanced MRI which highlighted multiple liver metastases present in all liver segments, with the largest metastases measuring 23 mm and enlarged retroperitoneal lymph nodes. On the 28th of May 2025 the patient underwent a full body contrast enhanced CT scan which detected 14 new pulmonary metastases plus the subpleural lesion detected 5 months earlier, which now measured 34/30/38 mm in size, and multiple retroperitoneal enlarged lymph nodes. Given the platinum eligible status of the patient and the rapid progression of the disease, he was initiated on the 10th of June 2025 on 8 courses of Gemcitabine/ Cisplatin chemotherapy over a period of 10 weeks - which he tolerated relatively well. During this time the

patient missed 2 courses of chemotherapy because of the side effects (mild pancytopenia and gastrointestinal symptoms).

Follow-up MRI performed on the 26th of September showed clinical response to chemotherapy with a reduction in size of the liver metastases and retroperitoneal lymph nodes. On October 2nd he underwent a new course of Gemcitabine/Cisplatin therapy and a follow up full body CT scan showed progression in size and number of the pulmonary metastases (18 lesions vs 15 lesions on the previous CT scan). Based on the rapid progression of the disease, the patient was scheduled for a PET CT scan on the 16th of October - which was not performed because in the meantime he developed neurological symptoms caused by multiple hemorrhagic brain metastases seen on brain CT scans. The patient was referred to the neurosurgical department where he died of multiple organ failure on the 13th of November 2025.

Current metastatic bladder guidelines recommend that platinum-based chemotherapy remains standard of care for eligible patients with pembrolizumab and other PDL-1 targeting agents reserved for ineligible patients with positive PDL-1 testing. Initial histopathological examination performed in 2018 did not reveal trophoblastic differentiation. Patient underwent annual CT scans after the initial surgery in 2018, which never indicated any signs of recurrence. Particular to this case was the rapid spread of metastatic bladder disease after a recurrence free period of 6 years, with transient response to chemotherapy followed by rapid progression. The atypical inguinal lymph node metastatic dissemination was most likely caused by deficient lymph drainage post radical cystectomy: during radical cystectomy extended pelvic lymph node dissection is performed which inhibits normal lymph drainage from the pelvic area.

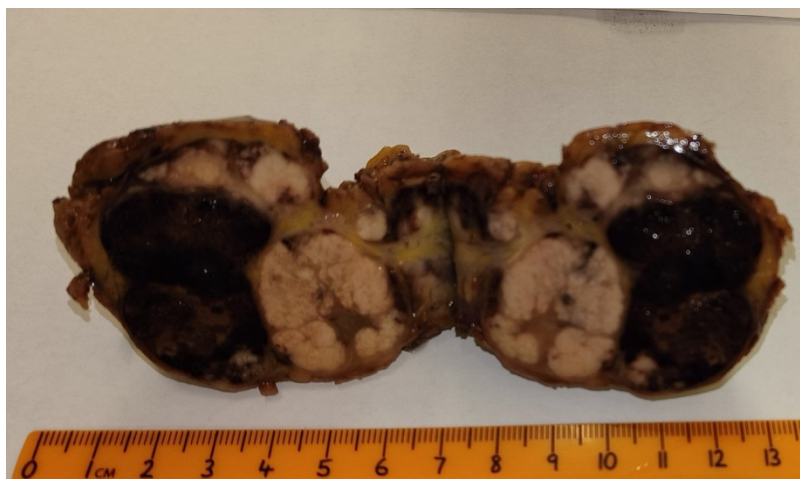


Fig. 5. Macroscopic aspect of left inguinal lymph node.

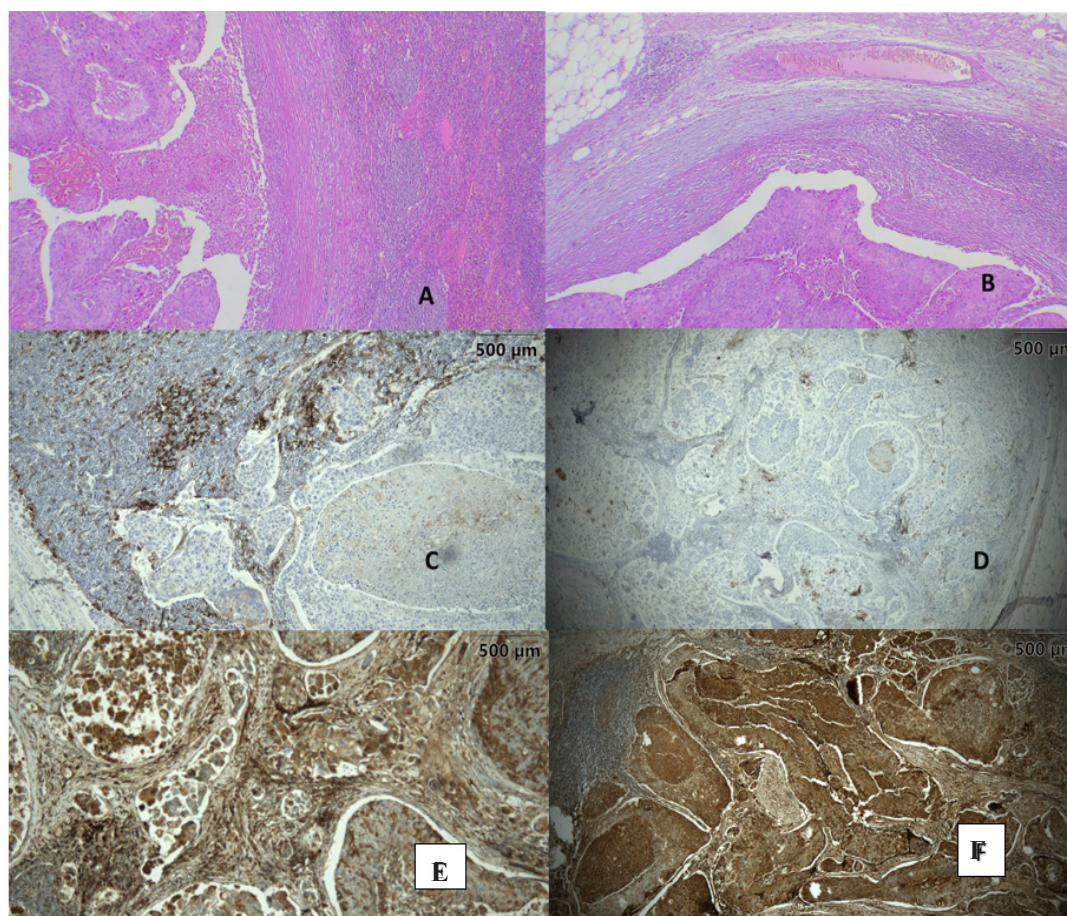


Fig. 6. A, B - Hematoxylin-eosin staining of lymphatic tissue; C, D - PDL-1 Positive staining; E, F - β -hCG positive staining.

Review

Introduction

Urothelial carcinoma with trophoblastic differentiation (UCTD) is an uncommon variant of urothelial carcinoma characterized by the presence of trophoblastic cells within a conventional urothelial carcinoma background [1]. Histologically, these tumors may contain syncytiotrophoblastic giant cells, β -hCG-producing tumor cells, or areas resembling choriocarcinoma [1-3]. Although trophoblastic differentiation has been recognized for several decades, the rarity of reported cases has limited understanding of its biological behavior and clinical significance [1-7]. Available evidence suggests that these tumors exhibit aggressive behavior, advanced stage at diagnosis, early metastases and poor prognosis compared with conventional urothelial carcinoma [1,3]. The objective of this review was to summarize the currently available evidence regarding the incidence, pathological features, treatment strategies, recurrence patterns, and survival outcomes of UCTD.

Methods

Study design

A systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement to identify published reports of urothelial carcinoma with trophoblastic differentiation.

Literature search

A comprehensive electronic literature search was performed in PubMed/MEDLINE, Scopus, Web of Science Core Collection, and Google Scholar from database inception to June 2026. The reference lists of all eligible articles were manually screened to identify additional relevant publications.

The following search strategy was adapted for each database:

("urothelial carcinoma" OR "bladder cancer" OR "transitional cell carcinoma")

AND

("trophoblastic	differentiation"	OR
"choriocarcinomatous	differentiation"	OR

“syncytiotrophoblastic giant cells” OR “ β -hCG” OR “human chorionic gonadotropin”).

For Google Scholar, the first 300 records sorted by relevance were screened using combinations of the keywords urothelial carcinoma with trophoblastic differentiation, urothelial carcinoma choriocarcinoma, β -hCG urothelial carcinoma, and syncytiotrophoblastic giant cells bladder. Only articles published in English were considered.

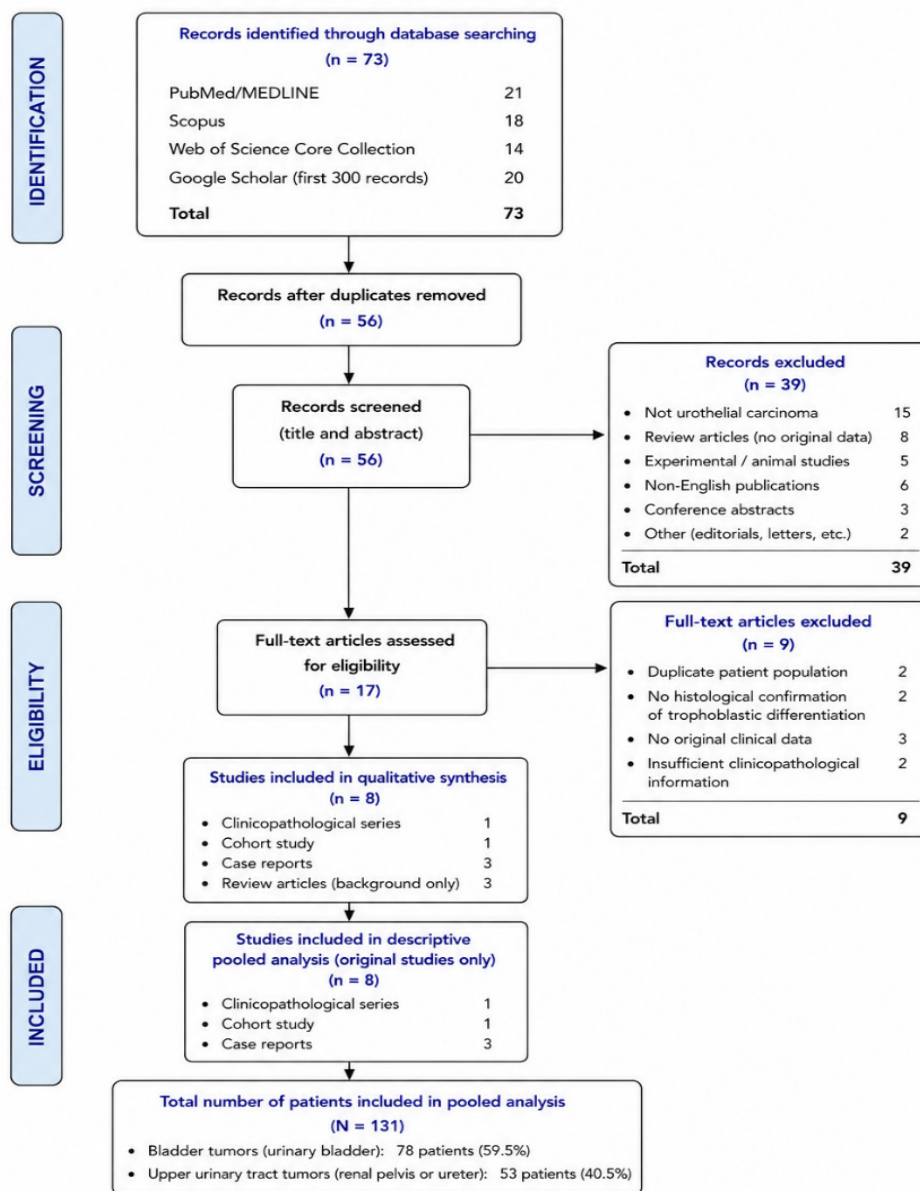
Eligibility criteria

Studies were eligible if they:

- reported histologically confirmed urothelial carcinoma with trophoblastic differentiation;
- contained original clinicopathological or outcome data;
- were published as case reports, case series, cohort studies, or clinicopathological studies.

PRISMA 2020 Flow Diagram for Systematic Review

Urothelial carcinoma with trophoblastic differentiation



Note: Review articles were included for background information and discussion only and were not part of the pooled analysis.

Fig. 7. Prisma flow chart.

The following publications were excluded:

- review articles without original patient data;
- conference abstracts;
- editorials and letters;
- experimental or animal studies;
- pure choriocarcinoma or germ-cell tumors;
- metastatic choriocarcinoma involving the urinary

tract;

- duplicate patient populations;
- non-English publications.

Study selection

After duplicate removal, two investigators independently screened titles and abstracts for eligibility. Full-text articles were subsequently reviewed. Disagreements were resolved by consensus.

The literature search identified 73 records (PubMed, $n = 21$; Scopus, $n = 18$; Web of Science, $n = 14$; Google Scholar, $n = 20$). After removal of 17 duplicate records, 56 studies underwent title and abstract screening. Thirty-nine studies were excluded because they were unrelated to urothelial carcinoma with trophoblastic differentiation, lacked original patient data, were review articles, conference abstracts, or were published in languages other than English. Seventeen full-text articles were assessed for eligibility. Nine articles were excluded after full-text review because they contained duplicate patient populations ($n = 2$), lacked histological confirmation of trophoblastic differentiation ($n = 2$), contained no original clinical data ($n = 3$), or provided insufficient clinicopathological information ($n = 2$). Ultimately, eight studies fulfilled the inclusion criteria and were included in the qualitative synthesis and descriptive pooled analysis.

Data extraction

The following variables were extracted whenever available: publication year, patient age and sex, tumor location, pathological stage and grade, presence of trophoblastic differentiation, β -human chorionic gonadotropin expression, treatment modality, recurrence, metastatic disease, follow-up duration, and survival status.

Outcomes

The primary outcomes of interest were the number of reported patients, clinicopathological characteristics, treatment modalities, recurrence patterns, metastatic disease, and survival outcomes. Secondary outcomes included the reported incidence of trophoblastic differentiation and the diagnostic utility of β -human chorionic gonadotropin immunohistochemistry.

Statistical analysis

Because the available literature consisted predominantly of case reports and small retrospective series with heterogeneous outcome reporting, a formal quantitative meta-analysis was not feasible. Data were therefore summarized using a descriptive pooled analysis. Continuous variables are presented as ranges or medians, whereas categorical variables are presented as frequencies and percentages.

Results

Eight studies fulfilled inclusion criteria [1-8]. These included: one clinicopathological series (16 patients) [1]; one cohort study (112 patients) [3]; three case reports [4,6,8]; three review articles [2,5,7]. A total of 131 patients with trophoblastic differentiation were identified (Fig. 7).

Incidence and prevalence

The largest study by Cheng et al. identified trophoblastic differentiation in 47 of 859 bladder urothelial carcinomas (5.5%) and 65 of 635 upper tract urothelial carcinomas (10.2%) [3]. These findings suggest that trophoblastic differentiation may be under-recognized in routine pathological practice. Most tumors were: high-grade, muscle-invasive, β -hCG positive and associated with lymphovascular invasion. Both bladder and upper urinary tract tumors were reported [1,3,4]. Regional and distant metastases were frequently described [1,3].

Treatment approaches for surgery eligible patients included: radical cystectomy; radical cystoprostatectomy; radical nephroureterectomy; metastasectomy in selected patients [8].

Systemic Therapy used with a neoadjuvant, adjuvant or palliative role included: cisplatin-based chemotherapy; carboplatin-based chemotherapy in patients with impaired renal function; immunotherapy and antibody-drug conjugates [6]. Han et al. reported complete radiological and biochemical response after treatment with tislelizumab and disitamab vedotin in advanced disease [6].

Mortality and Survival: available studies consistently reported worse outcomes compared with conventional urothelial carcinoma [1,3]. Przybycin et al. documented multiple cancer-related deaths despite treatment [1]. Cheng et al. demonstrated significantly increased risks of recurrence, progression, and cancer-specific mortality [3]. Because patient-level survival data were inconsistently reported, pooled five-year survival and pooled mortality rates could not be reliably calculated. Most recurrences reported in the literature occurred within the first few years after treatment [1,3,8]. No previously published case describing recurrence more than six years after radical cystectomy was identified.

Discussion

UCTD is an exceptionally rare variant of urothelial carcinoma. Although trophoblastic differentiation may be detected more frequently when immunohistochemistry is routinely used, clinically significant cases remain uncommon [1,3]. The available literature consistently demonstrates aggressive biological behavior. Most tumors are high-grade, muscle-invasive, and associated with increased risks of recurrence, metastases, and cancer-specific mortality [1,3]. These findings support the classification of trophoblastic differentiation as an adverse

prognostic feature. Diagnosis relies on histological examination and β -hCG immunohistochemistry. Serum β -hCG may be useful in selected patients for disease monitoring and follow-up [1,4]. Because no specific treatment guidelines exist, management currently follows principles used for high-risk urothelial carcinoma [9]. Radical surgery remains the cornerstone of treatment, while platinum-based chemotherapy, immunotherapy, and antibody-drug conjugates represent systemic treatment options for advanced disease [1,3,6,9]. β -hCG elevation with an inguinal or testicular mass in a patient with a bladder-cancer history should raise consideration of recurrent urothelial carcinoma with trophoblastic differentiation and not only a primary germ-cell tumor. The most notable finding of the present review is the apparent absence of previously reported recurrence occurring more than six years after radical cystectomy. EAU guidelines up until 2025 recommended annual cystoscopy in the absence of bladder recurrence in non-muscle invasive bladder cancer (NMIBC). The 2026 edition of the guidelines recommends life-long annual cystoscopies for NMIBC patients [10].

According to the 2026 EAU muscle invasive bladder cancer (MIBC) guideline, there is no fixed stopping time for oncological follow-up after radical cystectomy, including for patients treated for T2 bladder cancer. The guideline states that the exact time to stop follow-up is not well known and should be risk-adapted/individualized. For routine post-cystectomy cancer surveillance, the EAU panel suggests: CT chest/abdomen/pelvis every 6 months until year 3, then annual imaging thereafter. So, for a typical pT2N0 pure urothelial carcinoma after radical cystectomy, we should not interpret the guideline recommendation as “stop at 5 years.” A practical interpretation of follow-up schedules post radical cystectomy is:

- Years 1–3: CT every 6 months
- After year 3: annual imaging
- Beyond 5 years: individualized; EAU guidelines give no firm stop point

Longer surveillance is especially relevant if there are higher-risk features such as variant histology, positive lymph nodes, locally advanced disease, positive ureteral margins, CIS (carcinoma in situ)/multifocal disease, or high risk of upper-tract recurrence. EAU notes that locally advanced or node-positive patients may remain at recurrence risk for more than 20 years.

Limits of the review: based on the current available literature we can report incidence (5.5% and 10.2%), but we cannot reliably report prevalence, pooled mortality, or 5-year survival with and without treatment, because the published studies do not provide sufficiently complete patient-level outcome data [9]. Limits of the case report include the lack of TPS (Tumor Proportion Score) and CPS (Combined Positive Score) in the pathology report.

Also, this review did not include non-English literature, which could potentially be a source of language bias.

Conclusion

UCTD is a rare and highly aggressive variant of urothelial carcinoma characterized by high-grade pathology, invasive growth, metastatic potential, and poor oncological outcomes. Available evidence indicates increased recurrence and mortality compared with conventional urothelial carcinoma. Diagnosis requires careful pathological evaluation and immunohistochemical confirmation. Radical surgery and platinum-based systemic therapy remain the main treatment strategies, although emerging therapies may improve outcomes in selected patients. The newest follow-up strategies tend to emphasize the need for life-long surveillance in bladder cancer patients. The rarity of published cases continues to limit understanding of the disease. To our knowledge, our patient represents one of the few reported cases of recurrence occurring more than six years after radical cystectomy, highlighting the need for long-term surveillance even after prolonged disease-free follow-up.

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