

Systematic Review

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# Squamous cell carcinoma of the upper urinary tract in patients with urolithiasis: a systematic review

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## Abstract

**Aim:** To perform a systematic review on the current evidence about the squamous cell carcinoma (SCC) of the upper urinary tract in patients with urolithiasis.

**Methods:** A comprehensive bibliographic search on the MEDLINE, Scopus, Web of Science, and Cochrane Library databases was performed in December 2024. The SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type) framework was used to define inclusion criteria: male and female patients with urolithiasis (S); presence of SCC of the upper urinary tract (PI); prospective and retrospective studies (D); diagnosis based on imaging or pathological examination (E); qualitative, quantitative or mixed-methods (R). Quality of studies was assessed with Murad scale. Extracted data were synthesized in a narrative fashion. PROSPERO ID: "CRD42024625816".

**Results:** A total of 35 articles were included. Eight case series (22.9%) and 27 case reports (77.1%) were analyzed. The overall quality of papers was low. Sixty-three cases of SCC in patients with urolithiasis (range: 1-11) were identified. The male-to-female ratio was 1.55, with a median age of 60 years (range: 25-87). Most common symptoms included pain (70%), hematuria (60%), and infection (40%). Staghorn stones (48%) and multiple



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stones (42%) were the most frequently encountered types of calculi. Almost all SCCs (97%) developed in the calico-pyelic system. A radiological suspicion of SCC was raised using imaging in 64% of patients, while in 52% of cases it was an incidental finding during pathological examination after nephrectomy for a non-functional kidney. Locally advanced disease was observed in 44% of patients, while metastasis was reported in 16%. The overall prognosis was poor, with a survival of approximately 6 months and 1-2 years for metastatic and locally advanced cases, respectively.

**Conclusion:** The available evidence is poor because the disease is extremely rare and the literature is limited to isolated case reports and small series. Therefore, robust conclusions cannot be drawn. Only a limited number of cases are reported in the literature and the current data prevent the estimation of prevalence or reliable pathophysiologic hypotheses. However, this tumor appears to be associated with a severe prognosis. Further investigations are needed to explore the topic and provide sufficient evidence to formulate clear recommendations.

**Keywords:** Chronic inflammation, nephrolithiasis, squamous cell carcinoma, stones, urolithiasis, upper urinary tract

## INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a malignant neoplasm arising from the urothelium of the upper urinary tract, accounting for approximately 5%-10% of all urothelial carcinoma cases, with an estimated prevalence of two cases per 100,000 inhabitants<sup>[1]</sup>. These tumors are relatively uncommon yet highly malignant, originating from urothelial cells lining the renal calyces, renal pelvis, and ureters. While most upper urinary tract tumors are of the urothelial type, histological variants occur in up to 25% of cases<sup>[2]</sup>, each with distinct risk factors and epidemiological profiles that differ significantly from those of conventional bladder cancer<sup>[3,4]</sup>.

Among these histological variants, squamous cell carcinoma (SCC) of the upper urinary tract is particularly rare, accounting for only a small fraction of cases. Despite its low incidence, SCC seems to be associated with increased aggressiveness, significant diagnostic and therapeutic challenges, and overall poor prognosis<sup>[4]</sup>.

Some evidence suggests that SCC pathogenesis could be linked to chronic inflammation of the urinary tract epithelium. This process would initially induce squamous metaplasia of the urothelium, which may subsequently undergo malignant transformation into SCC. It has been hypothesized that, in the upper urinary tract, the primary etiological factor implicated in this transformation could be the presence of stones. In particular, long-standing untreated stone disease is believed to sustain chronic inflammation, providing a pathological substrate for the malignant transformation of the urothelium<sup>[5,6]</sup>.

Imaging findings of renal SCC range from solid renal masses to hydronephrosis, calcifications, and regional lymphadenopathy. However, these features are largely nonspecific, making it challenging to differentiate SCC from chronic inflammatory conditions such as xanthogranulomatous pyelonephritis or renal tuberculosis<sup>[3,7]</sup>.

Due to its rarity, SCC of the upper urinary tract remains poorly documented. Indeed, most available evidence derives from case reports and small case series, and topic-specific guidelines are lacking. Consequently, further research is essential to improve the understanding of this malignancy and optimize its management<sup>[8]</sup>.

The primary aim of this systematic review is to provide a comprehensive analysis of the current scientific evidence on SCC of the upper urinary tract in patients with renal and ureteral stone disease.

## MATERIALS AND METHODS

### Search strategy

A comprehensive bibliographic search was conducted in December 2024 using the MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify studies investigating the current evidence on SCC of the upper urinary tract in patients with urolithiasis. Different combinations of the following keywords were used in a title/abstract search, applying Boolean operators: *kidney, renal, pelvis, calyx, ureter, upper, urinary tract, UTUC, stone, calculi, lithiasis, urolithiasis, squamous, tumor, neoplasia, carcinoma*. Additionally, the reference lists of retrieved articles were manually screened to identify further relevant studies. The literature search was restricted to English-language articles and studies on human subjects. No restrictions were applied regarding the publication date.

### Study selection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>[9]</sup>. The SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type)<sup>[10]</sup> framework was used to define the inclusion criteria.

- (1) Sample (S): Male and female patients with urolithiasis;
- (2) Phenomenon of Interest (PI): Presence of SCC of the upper urinary tract;
- (3) Design (D): Prospective and retrospective studies (including case series and case reports);
- (4) Evaluation (E): Diagnosis based on imaging or pathological examination;
- (5) Research type (R): Qualitative, quantitative, or mixed-methods studies.

A two-step screening process was implemented. Initially, titles and abstracts were reviewed to identify potentially relevant studies. Full-text articles that met the inclusion criteria underwent a detailed assessment to confirm eligibility.

### Data extraction

The following data points were extracted from each included study: first author, publication year, country of origin, number of patients, age, sex, symptoms, stone characteristics, site of tumor, presence of hydronephrosis, radiological diagnosis of tumor, incidental diagnosis of tumor, microscopic findings, pathological stage, treatment of tumor, follow-up, and prognosis.

### Quality assessment

The level of evidence (LoE) was evaluated according to the Oxford Center for Evidence-Based Medicine 2011<sup>[11]</sup>. Study quality was assessed using the Murad scale<sup>[12]</sup> and arbitrarily categorized according to the total score as follows:

- (1) Low quality: 0-3 points;
- (2) Intermediate quality: 4-5 points;

(3) High quality: 6-8 points.

### Data analysis and synthesis

Due to the expected paucity, low quality, and heterogeneity of the available data, we decided not to perform a meta-analysis. Consequently, the results were reported in a narrative fashion. In particular, the extracted data were presented in the text and tables as shown in the original articles. However, when deemed necessary for a better overview, they were combined into sums, percentages, ranges, and medians.

### Other methodological details

The review methods were established before the study began, and the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the ID “CRD42024625816”. Study selection, data extraction, and quality assessment were performed independently by two authors (MS, ST), while a third author (CM) resolved any disagreements.

## RESULTS

A total of 35 articles were included in this review, comprising 8 case series (22.9%) and 27 case reports (77.1%) [Figure 1 and Table 1]. The studies collectively analyzed 63 patients, with a male-to-female ratio of 1.55 and a median age of 60 years (range: 25-87).

### Quality assessment

The methodological quality of the included studies was generally low. All studies corresponded to a Level of Evidence 4, reflecting the retrospective design and the predominance of case reports and small case series. According to the Murad scale, 29 studies (82.8%) were classified as low quality (score 0–3), 5 (14.3%) as intermediate quality (score 4–5), and only 1 (2.8%) as high quality (score  $\geq 6$ ). These findings highlight the limited robustness of the available evidence and the considerable risk of bias, which must be considered when interpreting the clinical and prognostic outcomes of this review.

Among the 8 case series, a total of 36 patients were identified. Sex was reported for 29 patients, of whom 17 were male (59%) and 12 were female (41%). The most frequently reported symptoms included pain (81%), hematuria (30%), and infection (51%). Regarding stone characteristics, staghorn calculi (62%) and multiple calculi (19%) were the most common types. Table 2 summarizes data from case series.

Among the 27 case reports, 17 men (63%) and 10 women (37%) were detected. The most commonly reported symptoms were pain (74.1%), hematuria (22%), and infection (22%). The most frequent types of stones were staghorn calculi (40.7%) and multiple calculi (29.6%). Table 3 presents findings from case reports.

Almost all SCCs (97%) developed in the calyceal-pelvic system. Hydronephrosis was observed in 54 patients (85.7%). A radiological suspicion of SCC was raised in 38% of cases, whereas in 44% it was incidentally detected during pathological examination after nephrectomy for a non-functional kidney.

### Pathological findings

Histological evaluation confirmed that the majority of tumors were pure SCC; although occasional cases with mixed histology (verrucous components) were described, studies reporting transitional variants were excluded from the analysis. Tumor grade was variably reported, with poorly differentiated forms prevailing among advanced cases. Pathological staging, available in a subset of patients, showed that 40% of patients presented with advanced disease [mainly pathologic T3-T4 (pT3-pT4), and, when available, node-positive

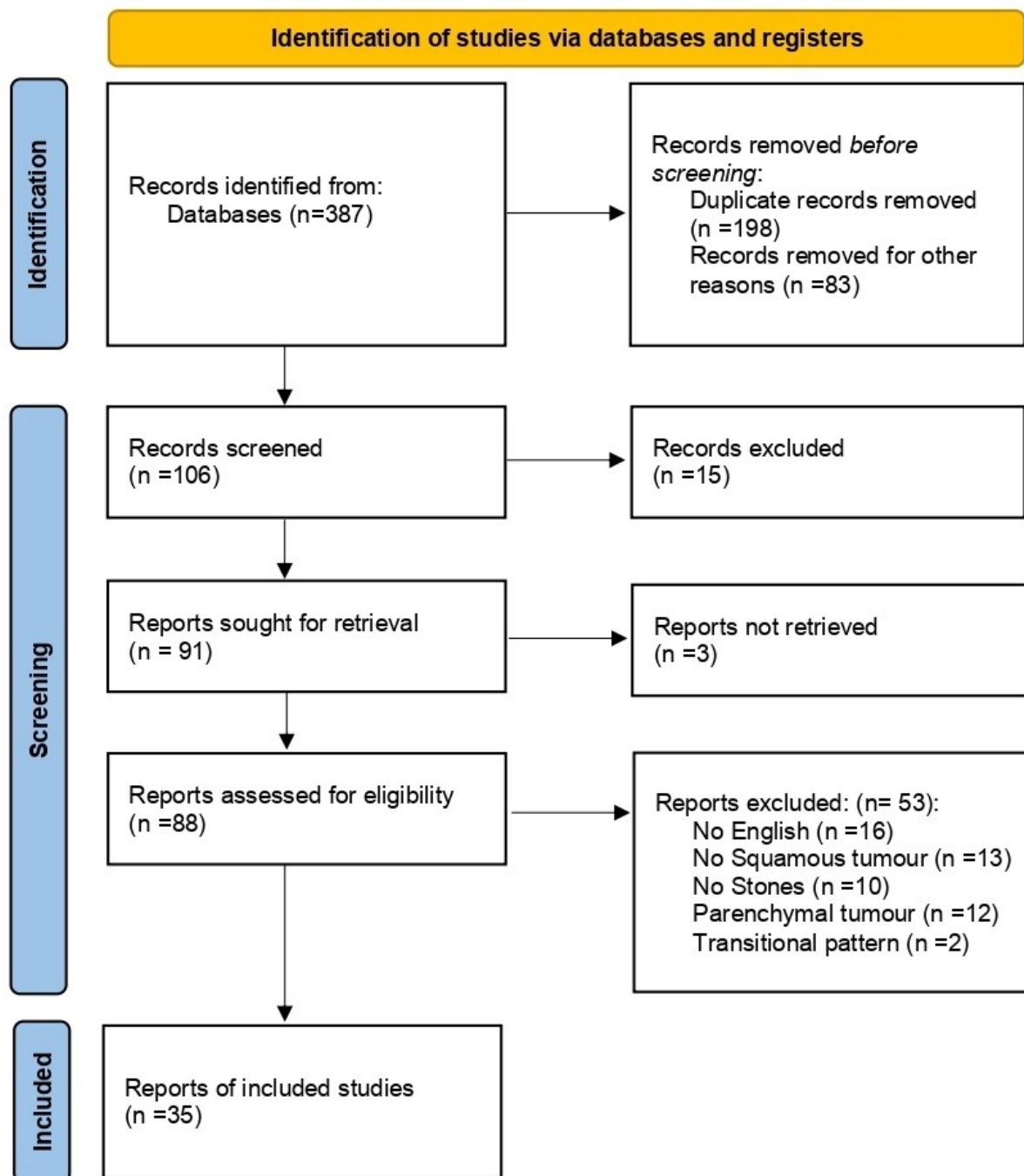


Figure 1. PRISMA flow diagram for study selection.

status (pN+)], while early-stage tumors (pT1-pT2) were rare and usually detected incidentally. Distant metastases were reported in 16% of cases. Lymph node involvement was inconsistently documented but, when present, was associated with adverse outcomes. Overall, advanced stage and poor differentiation correlated with long-standing staghorn calculi, hydronephrosis, and poor survival. Prognosis remained dismal, with a median survival of approximately 6 months in metastatic cases and 1–2 years in patients with locally advanced disease, whereas incidentally detected, well-differentiated tumors tended to show more favorable outcomes.

**Table 1. Main characteristics of the included studies**

First author, Publication year	Country of origin	Study design	Number of patients	Level of Evidence*	Quality of study**
Sözer, 1968 <sup>[13]</sup>	Turkey	Case report	1	4	1
Leong et al., 1976 <sup>[14]</sup>	China	Case series	3	4	2
Kinn, 1975 <sup>[15]</sup>	Sweden	Case series	6	4	2
Howat et al., 1983 <sup>[16]</sup>	England	Case report	1	4	2
Li and Cheung 1987 <sup>[17]</sup>	China	Case series	11	4	4
Mhiri et al., 1989 <sup>[18]</sup>	Tunisia	Case series	3	4	4
Narumi et al., 1989 <sup>[19]</sup>	Japan	Case series	4	4	3
Sheaff et al., 1996 <sup>[20]</sup>	England	Case report	1	4	3
Kimura et al., 2000 <sup>[21]</sup>	Japan	Case report	1	4	1
Kim et al., 2001 <sup>[22]</sup>	Korea	Case report	1	4	2
Sivaramakrishna et al., 2004 <sup>[23]</sup>	India	Case report	1	4	3
Ham et al., 2011 <sup>[24]</sup>	Korea	Case report	1	4	3
Jain et al., 2011 <sup>[4]</sup>	India	Case series	4	4	3
Verma et al., 2011 <sup>[25]</sup>	India	Case report	1	4	3
Paonessa et al., 2011 <sup>[26]</sup>	USA	Case report	1	4	2
Bhaijee, 2012 <sup>[3]</sup>	USA	Case report	1	4	3
Di Battista et al., 2012 <sup>[27]</sup>	Italy	Case report	1	4	3
Kalayci et al., 2013 <sup>[28]</sup>	Turkey	Case report	1	4	3
Jongyotha and Sriphradang, 2015 <sup>[29]</sup>	Thailand	Case report	1	4	4
Xiao et al., 2015 <sup>[30]</sup>	China	Case series	2	4	1
Nachiappan et al., 2016 <sup>[31]</sup>	India	Case report	1	4	2
Jakes et al., 2016 <sup>[32]</sup>	UK	Case report	1	4	2
Hassan and Qureshi, 2017 <sup>[7]</sup>	Pakistan	Case report	1	4	3
Deng et al., 2017 <sup>[33]</sup>	China	Case report	1	4	6
Kartal et al., 2019 <sup>[34]</sup>	Turkey	Case report	1	4	1
Sun and Li, 2020 <sup>[35]</sup>	China	Case report	1	4	1
Hosseinzadeh and Mohammadzadeh, 2020 <sup>[36]</sup>	Iran	Case report	1	4	5
Chaurasia, 2021 <sup>[37]</sup>	India	Case report	1	4	3
Terakawa et al., 2021 <sup>[38]</sup>	Japan	Case report	1	4	3
Oh and Kim, 2022 <sup>[39]</sup>	Republic of Korea	Case report	1	4	3
Liu et al., 2022 <sup>[40]</sup>	China	Case report	1	4	2
Patel et al., 2023 <sup>[41]</sup>	India	Case series	4	4	2
Priyatharsan et al., 2023 <sup>[42]</sup>	Sri Lanka	Case report	1	4	3
Alnefaie et al., 2024 <sup>[43]</sup>	SAU	Case report	1	4	2
Qiao et al., 2024 <sup>[44]</sup>	China	Case report	1	4	5

\*According to Oxford Center for Evidence-Based Medicine 2011; \*\*According to Murad scale.

## DISCUSSION

### Summary of findings

The collected case series and case reports highlighted the rare yet aggressive nature of SCC of the upper urinary tract; all cases included in this review were reported in association with urolithiasis. Therefore, the actual incidence of this condition among SCC of the upper tract cannot be determined. Most of patients

**Table 2. Main findings of included case series**

Reference	Age	N	Sex	Symptoms	Stone characteristics	Hydronephrosis	Site of SCC	Radiological diagnosis of SCC	Incidental diagnosis of SCC	Microscopic findings	Pathological stage	Treatment of SCC	Last Follow-up and prognosis
Leong <i>et al.</i> , 1976 <sup>[14]</sup>	56*	3	NA	Hematuria, mass, infection	NA	Yes	Upper calix	No	Yes	SCC	Metastatic	Nephrectomy	Death at: -13m DOD -1m DOC -1m DOC
Kinn, 1975 <sup>[15]</sup>	45* 60	6**	1M 1F	Fever, hematuria, infection, fistula, pain	Staghorn	Yes	RP	1 Yes 1 No	1 Yes 1 No	Poorly differentiated SCC	NA	Nephrectomy	Death at: -1y DOC -3m DOC -2m DOD
Li and Cheung 1987 <sup>[17]</sup>	60 69 73 69 45 62 43 60 67 65 45	11	5M 6F	Pain, mass, infection	Staghorn	Yes	RP	3 Yes	8 Yes	SCC	8 TxN+ 3 M1	Nephrectomy Nephroureterectomy, CT/RT	Death at: -3w -72m -2m -4m -1m -2w -7m -1m -5m -5m -1w
Mhiri <i>et al.</i> , 1989 <sup>[18]</sup>	57 47	2	2M	Pain, infection Pain, fever, mass	Staghorn in horseshoe kidney	Yes	RP RP	No	Yes	SCC	NA	Nephrectomy	-Death at 7m DOD -Death at 8m DOD
Narumi <i>et al.</i> , 1989 <sup>[19]</sup>	54 61 63 79	4	3M 1F	Pain, hematuria	NA	NA	2 Ureter 2 RP	4 Yes	No	SCC	<pT2N0 pT4N0 pT3N0 pT3N0	Nephrectomy	NA
Jain <i>et al.</i> , 2011 <sup>[4]</sup>	50 87 50 53	4	3M 1F	Pain, mass	Staghorn stones	Yes	RP	1 Yes	3 Yes	Well differentiated SCC 1 Poorly differentiated SCC	pT2N0M0 pT3N2cM0 pT3pN0Mx pT3N0M0	Nephrectomy + 2 CT	-NA -DOC -Alive a 3m NED -Alive at 5 m NED
Xiao <i>et al.</i> , 2015 <sup>[30]</sup>	55 61	2	1F, 1M	Pain, mass, hematuria	Multiple stones, bilateral	Yes	RP	2 Yes	No	Well differentiated SCC	T3N0M0 T3N0M0	Radical nephrectomy	-Death at 12m DOC -DOD

Patel <i>et al.</i> , 2023 <sup>[41]</sup>	61 25 79 77	4	2F, 2M	Pain, weight loss	Multiple stones	Yes	RP	3 No 1 Yes	3 Yes 1 No	SCC	T1bNOMx T1bNOMx T2NOM0 T3NOMx	3 Nephrectomy 1 Radical nephrectomy	NA
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\*Some ages were unavailable; \*\*Sex of some patients was unavailable. CT: Chemotherapy; NA: not available; RT: radiotherapy; SCC: squamous cell carcinoma; WD: with disease; NED: no evidence of disease; DOC: dead for other causes; DOD: dead for disease; RP: renal pelvis.

**Table 3. Main findings of included case reports**

Reference	Age	Sex	Symptoms	Stone characteristics	Hydronephrosis	Site of SCC	Radiological diagnosis of SCC	Incidental diagnosis of SCC	Microscopic findings	Pathological stage	Treatment of SCC	Last Follow-up and prognosis
Sözer, 1968 <sup>[13]</sup>	46	F	Pyuria, hematuria	Multiple stones	Na	Ureter	No	Yes	SCC	NA	Ureterectomy, RT	NA
Leong <i>et al.</i> , 1976 <sup>[14]</sup>	35	F	Pain, hematuria, infection	Staghorn stone	Yes	RP	No	Yes	Well differentiated SCC	pTxN+	Laparotomy, RT	Death at 4m
Sheaff <i>et al.</i> , 1996 <sup>[20]</sup>	41	M	Pain, fever	Stone in horseshoe kidney	Na	RP	No	Yes	Verrucous form of Well differentiated SCC	NA	Partial nephrectomy	Alive at 6m NED
Kimura <i>et al.</i> , 2000 <sup>[21]</sup>	48	M	Mass, hematuria	Staghorn stone	Yes	RP	Yes	No	SCC	M1	Biopsy + CT	Death at 1m DOD
Kim <i>et al.</i> , 2001 <sup>[22]</sup>	60	M	Pain, mass	Ureteral stone	Yes	RP, Ureter	No	Yes	SCC	NA	Nephroureterectomy	Alive at 36m NED
Sivaramakrishna <i>et al.</i> , 2004 <sup>[23]</sup>	46	M	Pain, fever, hematuria	Large renal stone	Yes	RP	Yes	No	SCC	NA	Nephroureterectomy, radiotherapy	Alive at 12m NED
Verma <i>et al.</i> , 2011 <sup>[25]</sup>	62	M	Pain, mass, fever	Multiple stones	Yes	RP	No	Yes	SCC	NA	Nephrectomy, CT	NA
Paonessa <i>et al.</i> , 2011 <sup>[26]</sup>	70	F	Pain	Multiple stones	No	RP	Yes	No	Poorly differentiated SCC	pT1-2	Nephrectomy	NA
Ham <i>et al.</i> , 2011 <sup>[24]</sup>	69	M	Pain, mass, weight loss	Multiple stones	Yes	RP	No	Yes	Poorly differentiated SCC	pT3NOM0	Nephrectomy	Death at 7m DOD
Bhaijee, 2012 <sup>[3]</sup>	77	F	Weight loss, anemia	Staghorn stone	Yes	RP	Yes	No	SCC in situ	pT3	Nephrectomy	Alive at 6m NED
Di Battista <i>et al.</i> , 2012 <sup>[27]</sup>	50	M	Hematuria, fever, mass	Multiple stones	Yes	RP	Yes	No	SCC	M1	Biopsy, RAE, CT	Death at 1m

Kalayci <i>et al.</i> , 2013 <sup>[28]</sup>	63	M	Weight loss,	Staghorn stones	Yes	RP, upper calix	Yes	No	Poorly differentiated SCC	pT3N0M0	Nephrectomy	NA
Jongyotha and Sriphrapradang, 2015 <sup>[29]</sup>	79	F	Weight loss, low mental status, pain	Staghorn stones	Yes	RP	Yes	No	SCC	M1	Biopsy + palliative care	Death at 1m
Nachiappan <i>et al.</i> , 2016 <sup>[31]</sup>	60	F	Pain, fever, infection	Staghorn stones	Yes	RP	Yes	No	SCC	PTx N0	Nephrectomy	NA
Jakes <i>et al.</i> , 2016 <sup>[32]</sup>	46	M	Pyuria, infection	Bilateral stones	No	RP	Yes	No	Well differentiated SCC	NA	Nephrectomy	NA
Hassan and Qureshi, 2017 <sup>[7]</sup>	45	M	Pain, infection	Multiple stones, impacted	Yes	RP	No	Yes	Mod differentiated SCC	pT3 Nx	Nephrectomy	NA
Deng <i>et al.</i> , 2017 <sup>[33]</sup>	61	M	Pain	Large stone	Yes	RP	Yes	No	Well differentiated SCC	pTxN+	Nephrectomy	Alive at 6m NED
Kartal <i>et al.</i> , 2019 <sup>[34]</sup>	38	F	Pain	Staghorn stones	Yes	RP	Yes	No	SCC	M1	Nephrectomy, CT	Death at 17m
Sun and Li, 2020 <sup>[35]</sup>	66	M	Pain, mass, ulcer	Large stone	Yes	RP	No	Yes	Mod differentiated SCC	M1	Nephrectomy, RT	Death at 3m
Mohammadzadeh, 2020 <sup>[36]</sup>	59	F	Pain, hematuria	Staghorn stones	Yes	RP	Yes	No	Well differentiated SCC	pT3	Radical nephrectomy	Death 12m DOD
Chaurasia, 2021 <sup>[37]</sup>	43	M	Pain	Multiple stones	Yes	RP	No	Yes	SCC	pT3NxMx	Nephrectomy	Alive at 12m
Terakawa <i>et al.</i> , 2021 <sup>[38]</sup>	74	F	Pain, malaise	Large, stone, ADPKD	No	RP	Yes	No	Well differentiated SCC	pT1-3	Nephrectomy, ileocecal resection	Death at 2m DOC
Oh and Kim, 2022 <sup>[39]</sup>	61	M	Pain	Staghorn stones	Yes	RP	Yes	No	Well differentiated SCC	pT4N0	Radical nephrectomy, hemicolectomy, LND	Alive at 6m
Liu <i>et al.</i> , 2022 <sup>[40]</sup>	54	F	Pain, mass	8mm stone	Yes	RP	Yes	No	SCC differentiated	NA	Radical nephrectomy, CT	Death at 7m DOD
Priyatharsan <i>et al.</i> , 2023 <sup>[42]</sup>	72	M	Pain, fever, weight loss	Staghorn stones	Yes	RP	Yes	No	SCC	pT4	Biopsy, palliative RT	NA
Alnefaie <i>et al.</i> , 2024 <sup>[43]</sup>	60	M	Pain, nausea,	Staghorn stones	Yes	RP	No	Yes	SCC	M1	Nephrectomy, fistula repair	NA
Qiao <i>et al.</i> , 2024 <sup>[44]</sup>	59	M	Infection	Multiple stones	Yes	RP	NA	NA	SCC	NA	RAE	NA

\*Some ages were unavailable; \*\*Sex of some patients was unavailable. CT: Chemotherapy; LND: lymph node dissection; NA: not available; PC: palliative chemotherapy; PR: palliative radiotherapy; RAE: renal artery

embolization; RT: radiotherapy; SCC: squamous cell carcinoma; WD: with disease; NED: no evidence of disease; DOC: dead for other causes; DOD: dead for disease; RP: renal pelvis.

presented with hematuria, pain, or mass effect, and a strong correlation was observed between SCC and the presence of staghorn or multiple calculi. At diagnosis, the disease was often locally advanced or metastatic, leading to poor outcomes despite surgical intervention. Treatment primarily involved nephrectomy or radical nephroureterectomy, sometimes combined with chemotherapy or radiotherapy, although no standard systemic therapy had been established. Although the available data should be interpreted with caution, as they mainly derive from advanced-stage cases, they suggest that SCC of the upper urinary tract is characterized by a generally poor prognosis.

### **Pathophysiological mechanisms**

The findings highlight a recurrent coexistence of stones and upper tract tumors, suggesting a potential relationship, although the strength of this association cannot be defined and the underlying mechanisms remain unclear. Several factors have been hypothesized to contribute to SCC development in the upper urinary tract.

(1) Mechanical Stimulation and Chronic Inflammation: persistent mechanical irritation from kidney stones led to chronic inflammation, which in turn promotes urothelial metaplasia, hyperplasia, and eventually malignant transformation<sup>[45-48]</sup>.

(2) Cytokines and Oxidative Stress: chronic inflammation triggers the release of cytokines, chemokines, and free radicals, which promote cellular damage, uncontrolled proliferation, and tumor growth<sup>[49]</sup>.

(3) Carcinogen Retention: urinary tract obstruction caused by stones may lead to prolonged exposure to potential carcinogens, accelerating tumor progression<sup>[39,41,44,50]</sup>.

In summary, kidney stones contribute to an environment of chronic inflammation, oxidative stress, and carcinogen exposure, creating favorable conditions for malignant transformation of the urothelium. Further molecular investigations are required to clarify these mechanisms.

Studies have not been able to identify specific environmental or occupational risk factors due to the limited accuracy in reporting this information. Regarding epidemiology, slight predominance of males over females has been observed, and the median age at diagnosis was 60 years.

Our review has confirmed that SCC of the upper urinary tract predominantly originated in the renal pelvis, with only a small percentage (3%) of cases affecting the ureter. The lower occurrence in the ureter had suggested that differences in epithelial exposure to irritants or site-specific immune responses may influence carcinogenesis<sup>[4,30]</sup>.

Additionally, SCC has been reported in kidneys with congenital or acquired abnormalities, including horseshoe kidney, ectopic kidney, polycystic kidney disease, and renal calyceal diverticula<sup>[51,52]</sup>. These findings suggested that structural anomalies may predispose certain individuals to chronic irritation and subsequent malignant transformation.

### Clinical management

Direct comparison with conventional UTUC could not be performed, as no control group was included in this review. However, this differs from clinical practice and guideline recommendations, where conventional urothelial carcinoma of the upper tract is used as the standard reference for assessing the prognostic and therapeutic implications of distinct histological entities such as SCC.

The frequent coexistence of large calculi and chronic inflammation may lead to an initial misdiagnosis as chronic pyelonephritis<sup>[3,37]</sup>. Moreover, SCC often presents insidiously, with symptoms frequently overlapping with those of urolithiasis, including flank pain and hematuria. This nonspecific clinical picture makes early recognition difficult, often leading to a delayed diagnosis. Consequently, in most cases, SCC is detected incidentally following nephrectomy for a non-functioning kidney rather than through preoperative imaging findings<sup>[53,54]</sup>.

In several studies<sup>[21,27,29,42,44]</sup>, the diagnosis of SCC has been made through biopsies. Therefore, in cases of suspicious stone-related lesions observed during surgery, it is advisable to perform multiple histological biopsies.

Despite advances in imaging techniques, SCC remains challenging to detect radiologically. Ultrasound and computed tomography (CT) scans often fail to differentiate SCC from chronic inflammatory conditions, leading to misinterpretation or underestimation of the disease burden<sup>[19,28]</sup>. Although contrast-enhanced CT can provide valuable insights into tumor extent, its diagnostic accuracy remains limited, particularly in patients with chronic kidney disease who cannot undergo contrast studies. Furthermore, urine cytology has low sensitivity due to the presence of stones, which may prevent tumor cell shedding into the urinary tract or may cause confounding inflammatory changes in the exfoliated cells<sup>[44,55]</sup>.

Given these diagnostic challenges, periodic imaging evaluations, particularly in patients with long-standing urolithiasis, hydronephrosis, or renal dysfunction, should be considered.

Therapeutic approaches remain non-standardized, with radical nephroureterectomy and lymph node dissection being the preferred surgical strategy. However, due to frequent late-stage presentation, surgery alone rarely improves long-term survival. Unlike urothelial carcinoma, where chemotherapy and immunotherapy have improved outcomes, no systemic therapies have been established for SCC. Although radiotherapy and chemotherapy have been attempted in select cases, their efficacy remains largely uncertain, underscoring the urgent need for further research into targeted therapies<sup>[17,46]</sup>.

### Prognosis

The prognosis of SCC of the upper urinary tract is markedly worse than that of urothelial carcinoma (UTUC), largely due to the frequent occurrence of delayed diagnosis, limited systemic treatment options, and the aggressive biological behavior of the tumor<sup>[4,39]</sup>. In our review, most patients were diagnosed at an advanced stage, with local invasion or distant metastases present in a significant proportion of cases (44% and 16%, respectively).

Where available, survival data revealed median overall survival (OS) ranging between 5 and 7 months in patients with metastatic disease, and 12 to 24 months in those with locally advanced but non-metastatic disease. Disease-free survival (DFS) was rarely reported in the literature, but isolated case reports indicated recurrence within 2 to 8 months after surgery in several patients with high-grade tumors.

Only a minority of patients - fewer than 10% - achieved survival beyond 5 years. Long-term survivors were more likely to have been diagnosed incidentally at an early stage and to have undergone radical surgery without evidence of lymphovascular invasion or metastasis at presentation<sup>[4,55]</sup>.

Several potential prognostic factors were identified:

- (1) Tumor stage at diagnosis: Strongly associated with survival, with metastatic cases faring worst.
- (2) Histological grade: Particularly poorly differentiated tumors, correlated with shorter OS.
- (3) Mode of diagnosis: Patients with incidentally discovered tumors following nephrectomy for presumed benign conditions had better outcomes than those diagnosed based on imaging.
- (4) Stone burden: Presence of staghorn calculi and prolonged stone disease was frequently associated with delayed diagnosis and more advanced disease.

In contrast, UTUC generally has a more favorable prognosis when detected early, supported by the availability of standardized staging, risk stratification systems, and established systemic treatments including chemotherapy and immune checkpoint inhibitors.

These findings underscore the urgent need for earlier detection, consistent staging, and more effective systemic therapies in this patient population.

### **Strengths, limitations, and future directions**

To the best of our knowledge, this is the first systematic review specifically investigating the association between upper urinary tract SCC and urolithiasis. It provides a comprehensive synthesis of the existing evidence and highlights recurring clinical and radiological patterns in a condition that remains poorly understood. This work offers a valuable reference point for clinicians and researchers confronted with this rare malignancy.

The main limitation of the available literature is the predominance of low-quality retrospective evidence, primarily composed of isolated case reports and small case series, which limits the generalizability of findings and hinders the development of evidence-based recommendations. Additionally, there is a lack of standardized reporting regarding imaging findings, pathological details, and follow-up outcomes across the included studies.

- (1) Future research should focus on clearly defined and feasible objectives, including the establishment of multicenter registries or collaborative databases to systematically collect data on SCC cases in patients with urolithiasis;
- (2) Prospective studies assessing the incidence of SCC in high-risk populations (e.g., those with long-standing staghorn stones or non-functioning kidneys);

- (3) Implementation of standardized imaging protocols and diagnostic algorithms aimed at distinguishing SCC from chronic pyelonephritis or xanthogranulomatous pyelonephritis;
- (4) Histopathologic and molecular profiling studies to identify biomarkers that may enable earlier diagnosis or serve as therapeutic targets;
- (5) Clinical trials or retrospective cohort analyses evaluating the effectiveness of systemic treatments (e.g., chemotherapy, immunotherapy) in SCC of the upper tract, possibly adapted from urothelial carcinoma protocols.

Clarifying the pathophysiologic mechanisms linking chronic inflammation, urolithiasis, and malignant transformation of the urothelium will also be critical. A deeper mechanistic understanding could support the development of targeted preventive strategies, such as timely surgical treatment of high-risk stone disease and surveillance imaging in selected patients.

Ultimately, strengthening the quality of evidence through well-structured research will be essential to guide clinical decision-making and allow for the development of specific diagnostic and therapeutic guidelines.

In conclusion, SCC of the upper urinary tract is an exceptionally rare and aggressive malignancy, most frequently associated with chronic and complex urolithiasis. Its nonspecific clinical features and overlap with benign conditions often result in delayed or incidental diagnosis, which contributes to a generally poor prognosis. The current literature is limited to low-quality retrospective studies, mostly case reports and small series, which hinders the ability to draw definitive conclusions regarding epidemiology, pathogenesis, and optimal management. Furthermore, there is a lack of validated diagnostic algorithms and no standardized systemic therapies tailored to SCC of the upper urinary tract. Clinicians should maintain a high index of suspicion in patients with long-standing staghorn or infected stones, particularly in the setting of a non-functioning kidney. However, given the scarcity of robust evidence, caution is warranted in extrapolating management strategies from other urologic malignancies. Future research should prioritize prospective multicenter data collection, improved radiologic and histopathologic diagnostic protocols, and translational studies aimed at identifying molecular targets. High-quality studies are needed to clarify the natural history of the disease, define risk factors, and guide the development of evidence-based clinical guidelines.

## DECLARATIONS

### Authors' contributions

Conceptualization: Stizzo M, Manfredi C

Study selection: Stizzo M; Tammaro S

Data extraction: Stizzo M, Tammaro S

Manuscript writing: Stizzo M, Tammaro S, Rubinacci A

Quality assessment: Stizzo M, Tammaro S, Arcaniolo D, Spirito L, Goumas IK, Giusti G, Puliatti S, Tailly T

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Manuscript writing: Rubinacci A

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All authors made substantial contributions to the manuscript and approved its final version.

#### **Availability of data and materials**

All reported data are available in the selected articles. Raw results of the bibliographic search and study selection process are available upon justified request to the corresponding author.

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All authors declared that there are no conflicts of interest.

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Not applicable.

#### **Consent for publication**

Not applicable.

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