Original Article

Application of warning biopsies in percutaneous nephrolithotomy

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Background: At present, few articles on percutaneous nephrolithotomy (PCNL) for renal calculi and renal pelvic tumors detected by intraoperative biopsy exist, which has provided limited guidance for clinical practice. In this article, we aimed to further study the relationship between renal calculi and renal pelvic tumors.

Methods: We retrospectively analyzed the medical records of patients with abnormal mucosal biopsy results who underwent PCNL for kidney stones in the Urology Department of Peking University People's Hospital from January 2011 to November 2021.

Results: In total, 2,801 patients underwent PCNL for kidney stones, of whom 69 underwent intraoperative mucosal biopsy. Biopsy results indicated that 8 cases were malignant (11.60%), and 61 cases were benign (88.40%). All malignant cases were renal pelvic carcinoma. Seven were urothelial carcinoma, and one of these was urothelial carcinoma with squamous differentiation. Only one was squamous cell carcinoma. The preoperative information of patients with a malignant mucosa biopsy was analyzed. To provide clinical guidance, an early warning biopsy system was established based on the abnormal mucosa found during the operation. We found that PCNL should be considered if the following risk factors are associated with stones: advanced age, long history of kidney stones, severe hydronephrosis, urinary tract infection, multiple or staghorn stones.

Conclusions: Early warning information should be established for patients with kidney stones based on preoperative clinical characteristics and intraoperative mucous membrane observations. An early warning biopsy should be performed for patients with possible tumors to detect tumors in a timely manner and provide early treatment to improve patient prognosis.

Keywords: Percutaneous nephrolithotomy (PCNL); warning biopsy; renal pelvis tumor; kidney stone; mucosal

Submitted Feb 18, 2024. Accepted for publication Jun 26, 2024. Published online Aug 26, 2024.
doi: 10.21037/tau-24-91
View this article at: https://dx.doi.org/10.21037/tau-24-91

Introduction

Urolithiasis is a common disease of the urinary system, and many studies have shown a close relationship between calculi and tumors (1-3). Meta-analyses by Cheungpasitporn *et al.* (1) and a cohort study by van de Pol *et al.* (2) concluded that patients with kidney stones had a significantly increased risk of renal cell carcinoma (RCC) and upper urinary tract transitional cell carcinoma compared with patients without a history of kidney stones. A cohort study by Lin *et al.* (3) showed that patients diagnosed with stones had a 1.82-fold higher risk of developing urothelial cancer. The risk of kidney tumor is greatly increased in patients with kidney stones. Therefore, malignant kidney tumors should be

suspected in patients with kidney stones, and a biopsy of possible abnormal mucosa should be taken, in combination with assessing the preoperative clinical characteristics and percutaneous nephrolithotomy (PCNL) findings. Therefore, the presurgical clinical characteristics of patients constituted our early warning information, and an early warning system was established using the presurgical data in combination with intraoperative abnormal mucous membrane observations. Suspicious mucous membranes observed microscopically were biopsied, i.e., an early warning biopsy. Establishment of an early warning system is to further study the relationship between renal calculi and renal pelvic tumors. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-91/rc).

Methods

General information

Clinical data of 2,801 patients with renal calculi who underwent PCNL in the Department of Urology, Peking University People's Hospital from January 2011 to November 2021 were retrospectively collected. The date of the pathological biopsy was the start time of follow-up, and the follow-up end point was December 1, 2022. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Peking University People's Hospital (No. 2024PHB170-001). Informed consent was obtained from all participating patients.

The following were considered normal ranges of laboratory test results: urine white blood cell (WBC) count, 0–9/μL; urine red blood cell (RBC) count, 0–12/μL; serum creatinine level: male 59–104 μmol/L, female 45–84 μmol/L; and urine bacterial count: male 0–42/μL, female 0–930/μL.

Statistical analysis

The statistical software SPSS (version 26.0) was used for statistical analysis. Quantitative data are expressed as medians and interquartile ranges, and qualitative data are expressed as frequencies and percentages.

Operative method

All patients were placed in the prone position, with routine disinfection and draping. Under ultrasound guidance, the renal calyces were punctured in the posterior axillary line under the subcostal region. After urine was observed, the guidewire was inserted, the cannula was dilated, and a nephroscope and ultrasound probe were inserted. The stones were removed by pneumatic ballistic and holmium laser lithotripsy. After lithotripsy, the renal pelvic mucosa was observed under nephroscopy if the following abnormalities were found: mucosal hydropathy lesions, pedicled papillary masses, villous or polypoid masses, local mucosal lichenoid changes, or abnormal mucosal color of the kidney stone site. Mucosal biopsy forceps were used to extract a sample from the target area. Finally, a guidewire was inserted, the ureteral catheter was removed, ureteral stent was inserted under direct vision, and a nephrostomy tube was placed.

Results

A total of 69 patients underwent intraoperative mucosal biopsy, including 40 males and 29 females. The median follow-up time was 3.80 (0.27, 7.82) years. Among them, 34 (49.30%) had bilateral renal calculi, 11 (15.90%) had right renal calculi, 24 (34.80%) had left renal calculi, 38 (55.10%) underwent a left renal mucosal biopsy, and 30 (43.50%) underwent a right renal mucosal biopsy; one case underwent a bilateral renal biopsy. In total, 67 cases of preoperative hydronephrosis (95.71%) were observed.

Highlight box

Key findings

- If patients with kidney stones have the following factors, they should be suspected and undergo examination for renal pelvic tumors: advanced age, long history of kidney stones, severe hydronephrosis, urinary tract infection and kidney stone types.

What is known and what is new?

- The clinical characteristics of patients with malignant renal pelvis biopsy results are unknown.
- It is known that patients with renal calculi may be associated with renal pelvic tumors.

What is the implication, and what should change now?

- Renal pelvis mucosa should be carefully examined in patients with renal calculi undergoing percutaneous nephrolithotomy (PCNL). Renal pelvis mucosa biopsy is recommended if there is any abnormality or if the above five risk factors are combined.
- More data of patients undergoing PCNL for renal calculi with intraoperative renal pelvic mucosal biopsy are needed to obtain more convincing statistical data.

Figure 1 A microscopic view of abnormal mucosa in a patient with urothelial carcinoma (UC) (high-grade) (8 times magnification).

Biopsy results indicated that 8 cases were malignant (11.60%), and 61 cases were benign (88.40%). All malignant cases were renal pelvic carcinoma. Seven were urothelial carcinoma (the intraoperative nephroscopic findings in one of these cases are shown in *Figure 1*, 8 times magnification), and one of these was urothelial carcinoma with squamous differentiation. Only one was squamous. There is only one was squamous cell carcinoma. The general patient data are shown in *Table 1*.

Detailed clinical data of eight cases of patients with malignant are shown in *Table 2*.

Discussion

At present, few articles on PCNL for renal calculi and renal pelvic tumors detected by intraoperative biopsy exist, which has provided limited guidance for clinical practice. This is the largest report of PCNL biopsy results for renal calculi and the most complete case report of calculi complicated by tumors from a single center. Yeh *et al.* studied the pathological results of non-functioning kidneys caused by kidney stones after nephrectomy and found that up to 51.06% of patients were diagnosed with malignant tumors after surgery. Among these patients, only 29.00% were suggested to have malignant renal tumors on preoperative imaging (4). In this study, only one of eight cases of renal pelvic carcinoma indicated tumors on preoperative imaging, and the remaining seven cases were diagnosed on intraoperative mucosal biopsy. Preoperatively diagnosing visible kidney tumors in patients with kidney stones is relatively difficult, for the following reasons. First, the symptoms of a renal pelvic tumor are masked by the severe pain of urinary calculi. Second, preoperative hydronephrosis, chronic inflammation, and infection makes finding tumors in the renal pelvis on preoperative imaging, including enhanced computed tomography (CT), difficult (5,6). Third, patients with renal insufficiency cannot undergo enhanced CT examination or venography (5). Fourth, due to kidney stone obstructions, tumor cells cannot be discharged through the urinary tract, resulting in a low urine cytology positivity rate (5,6). This group of eight patients had a preoperative urinary tract CT, plain film of kidney-ureter-bladder (KUB), and B-scan ultrasonography to wait in line, but only one patient was suspected of having a renal pelvic tumor, and the rest were not suspected of having a combination of kidney stones and tumors (preoperative CT images of some cases are shown in *Figure 2*). Therefore, making a definite preoperative diagnosis in patients with renal calculi and pelvic tumors is often difficult, and early warning biopsies should be performed. The patient's preoperative clinical characteristics, such as the history of kidney stones, hydronephrosis, and urinary tract infections, were combined with intraoperative findings to establish an early warning system, and suspicious results underwent mucosal biopsy to allow early detection and treatment to improve the patient prognosis.

The relationship between kidney stones and renal pelvic tumors is unclear. The possible reasons include the following. First, kidney stones with long-term mechanical stimulation of mucous membranes cause local chronic inflammation and infection, resulting in urinary epithelial cell proliferation changes, including regeneration, metaplasia, and hyperplasia. Second, local inflammatory cells secrete cytokines, chemokines and free radicals produced by oxidative stimulation to promote tumor growth (6). Third, kidney stones that cause an obstruction allow carcinogens to function for a long time in the epithelium of the urinary tract, accelerating the tumor progression (5). According to previous studies (5,6), renal calculi combined with hydronephrosis and urinary tract infections have been suggested as risk factors for the occurrence of renal pelvic tumors, and such patients should be aware of the possibility of kidney stones combined with kidney tumors. In addition, if patients with kidney stones have the following factors, they should be suspected and undergo examination for renal pelvic tumors:

Table 1 Clinical characteristics of patients who underwent mucosal biopsy

Clinical characteristics	Male (n=40)	Female (n=29)
Urine white blood cell (/μL)	97.50 (26.00, 912.50)	552.00 (85.50, 1,585.50)
Urine red blood cell (/μL)	61.50 (11.25, 397.50)	30.00 (15.00, 80.00)
Urine bacterial count (/μL)	24.00 (8.00, 622.00)	586.00 (46.00, 3,254.00)
Urine pH	6.00 (5.63, 6.88)	6.25 (6.00, 6.50)
Urine nitrite (number of patients)		
Positive	6 (15.00)	8 (27.60)
Serum creatinine (μmol/L)	85.00 (73.00, 102.25)	84.00 (59.50, 179.00)
Urine culture (number of patients)		
Positive	8 (20.00)	16 (55.17)
Stone diameter (cm)	2.30 (2.00, 3.625)	3.00 (2.00, 4.05)
Degree of hydronephrosis		
Mild	9 (22.50)	7 (24.10)
Moderate	11 (27.50)	7 (24.10)
Severe	13 (32.50)	11 (37.90)
History of kidney stones (months)	30.00 (2.00, 120.00)	67.00 (6.75, 177.00)

Data are presented as M (P25, P75) or n (%). Hydronephrosis grading (according to the results of CT images): (I) no hydronephrosis: anteroposterior diameter of renal pelvis ≤10 mm, no dilatation of renal calices; (II) mild hydronephrosis: anteroposterior diameter of renal pelvis >10 mm, ≤20 mm, no dilatation of renal calices; (III) moderate hydronephrosis: anteroposterior diameter of renal pelvis >20 mm, ≤30 mm, accompanied by calyceal dilatation; (IV) severe hydronephrosis: anteroposterior diameter of renal pelvis >30 mm, accompanied by thinning of renal cortex. CT, computed tomography.

(I) Advanced age: the average age of the eight patients with malignant tumors in this group was 60.40 years, and seven patients were older than 50 years, as shown in *Table 2*;

(II) Long history of kidney stones: 6 cases (75.00%) had a history of kidney stones of more than 1 year, as shown in *Table 2*, and almost all patients with combined pelvic malignant tumors had a history of kidney stones of >1 year. A small kidney stone burden may cause no symptoms, and the kidney stone history may actually be longer;

(III) Severe hydronephrosis: this study had 5 cases (62.50%) of severe preoperative hydronephrosis. In a case report by He *et al.* (5), 5 patients had severe hydronephrosis;

(IV) Urinary tract infection: in this study, 5 cases (62.50%) were complicated with urinary tract infections. Of the 21 patients in *Table 3*, 10 patients did not mention whether or not they had a urinary tract infection; of the other 11 patients, 9 (81.82%) had urinary tract infections;

(V) Kidney stone types: the eight patients in this study had multiple stones. In the cases reported in *Table 3*, eight patients had multiple stones and nine patients had staghorn stones. In a report by An *et al.*, four of six patients had multiple or staghorn stones (6). Considering that multiple stones and staghorn calculi have larger renal pelvic mucous membrane contact areas, the stronger stimulation of the renal pelvic mucous membranes causes more serious outflow obstructions.

Because diagnosing renal calculi complicated by renal tumors before surgery is difficult, it is necessary to carefully and comprehensively explore the mucosa of various parts of the renal pelvis during PCNL in patients with renal calculi and the above risk factors. Mucosal biopsy during PCNL is an effective and accurate auxiliary diagnostic method; however, no unified indication for mucosal biopsy currently exists. Based on previous case reports and the eight patients in this study, we summarized the mucosal abnormalities

Table 2 Clinical characteristics of patients with renal pelvic carcinoma

Sex	Age (y)	History of stones (y)	Degree of hydronephrosis	Ipsilateral surgery	Urinary infection	Stone type	Biopsy pathology	Treatment	Follow-up
Male	65	1	Mild + renal cyst	Yes	No	Multiple	Papillary high-grade UTUC	Endoscopic resection	12 m, until FTD
Female	40	10	Severe	Yes	Yes	Staghorn	High-grade UTUC	Neoadjuvant chemotherapy (GC) and RNU	7 m, then lost to follow-up
Male	67	20	NA	No	No	Staghorn	High-grade UTUC with squamous differentiation	Endoscopic ablation and neoadjuvant chemotherapy (GC)	2 m, until FTD
Male	56	3	Severe	Yes	Yes	Multiple	Squamous cell carcinoma	Renal artery embolization	NA
Male	50	3	Severe	Yes	Yes	Multiple	Low-grade UTUC	RNU and adjuvant chemotherapy (GC)	3.79 y (died of lung metastasis)
Female	68	20	Moderate	Yes	Yes	Staghorn	Low-grade UTUC with high grade component	Endoscopic resection	10.90 y until FTD
Male	58	0.25	Severe	No	No	Multiple	Low-grade UTUC with high grade component	RNU	10.84 y until FTD
Male	79	0.25	Severe + renal cyst	Yes	Yes	Multiple	UTUC	Renal artery embolization	2 m, then died of other causes

Hydronephrosis grading (according to the results of CT images): (I) no hydronephrosis: anteroposterior diameter of renal pelvis ≤10 mm, no dilatation of renal calices; (II) mild hydronephrosis: anteroposterior diameter of renal pelvis >10 mm, ≤20 mm, no dilatation of renal calices; (III) moderate hydronephrosis: anteroposterior diameter of renal pelvis >20 mm, ≤30 mm, accompanied by calyceal dilatation; (IV) severe hydronephrosis: anteroposterior diameter of renal pelvis >30 mm, accompanied by thinning of renal cortex. y, years; m, months; UTUC, upper tract urothelial carcinoma; FTD, follow-up termination date; GC, gemcitabine + cisplatin; RNU, radical nephroureterectomy; NA, not available; CT, computed tomography.

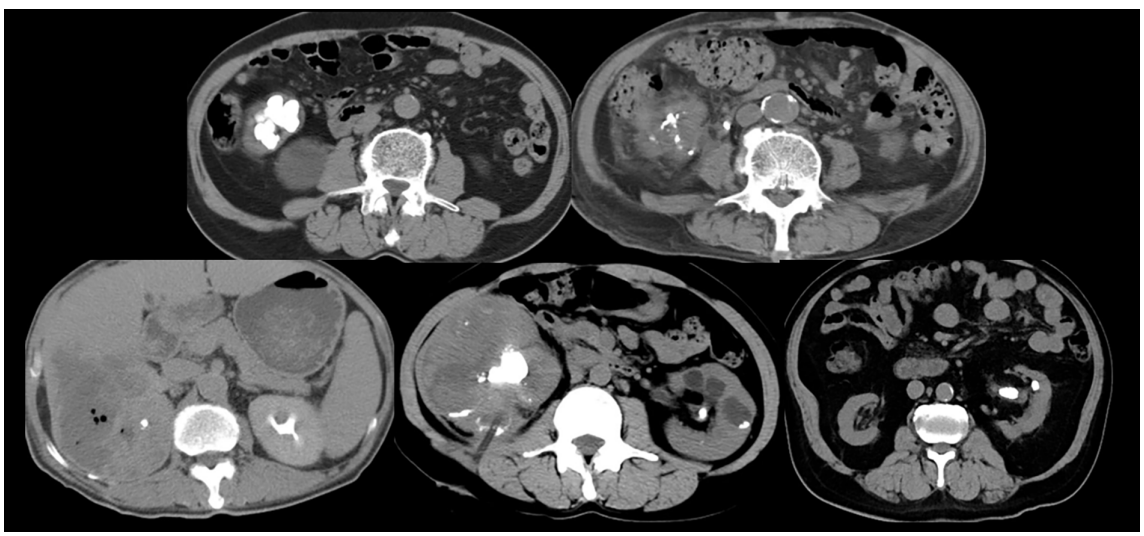

Figure 2 Preoperative computed tomography (CT) images of selected patients.

Table 3 Literature regarding patients with kidney stones and tumors and clinical characteristics of patients in case reports

Authors	Number of cases	Sex	Age (y)	History of stones	UTI	Stone type	Treatment	Pathology	Follow-up
Nakano *et al.* (7)	1	Male	70	NA	NA	Stones in calyceal diverticula	RNU	SCC + UC	5 y, no progression
Xiao *et al.* (8)	2	Female	55	10 y	Yes	Single	Radical nephrectomy	SCC	12 m, died of metastatic liver tumor
		Male	61	5 y	Yes	Single	Radical nephrectomy	SCC	NA, died of severe pulmonary infection complication
Kumar *et al.* (9)	1	Male	75	30 y	No	Multiple	Radical nephrectomy	SCC	3 m, no progression
Wu *et al.* (10)	2	Male	77	2 y	NA	Staghorn	PCNL → nephrectomy	SCC	1 m, died of metastatic disease
		Female	54	5 y	NA	Staghorn	PCNL → palliative treatment	SCC	3 m, died of severe complications
Kivlin *et al.* (11)	1	Male	77	Many years	Yes	Staghorn	Nephrectomy	SCC	NA
Kondisetty *et al.* (12)	1	Female	60	NA	Yes	Staghorn	Nephrectomy → chemotherapy	SCC	16 m, died of tumor progression
Hosseinzadeh *et al.* (13)	1	Female	59	14 m	No	Staghorn	Radical nephrectomy	SCC	1 y, died of tumor progression
Kasahara *et al.* (14)	1	Female	70	NA	Yes	Staghorn	Nephrectomy	SCC	2 m, died of tumor progression
Tsuboi *et al.* (15)	1	Male	66	20 y	Yes	Staghorn	ECIRS → chemotherapy and pembrolizumab	UC	7 m, died of tumor progression
Chang *et al.* (16)	1	Female	69	Many years	Yes	Staghorn	Radical nephrectomy	SCC	4 m, no progression
Aggarwal *et al.* (17)	1	Male	54	10 m	Yes	Multiple	RNU	UC	1 y, died of tumor progression
Yu *et al.* (18)	1	Female	64	1 y	NA	Multiple	laparoscopic nephrectomy	RCC	3 m, died of tumor progression
Liu *et al.* (19)	1	Female	54	6 m	NA	Multiple	Radical nephrectomy and chemotherapy	SCC with dedifferentiated sarcomatosis	7 m, died of tumor metastases
Huang *et al.* (20)	1	Male	82	NA	NA	Multiple	Radical nephrectomy	SCC	10 m, died of tumor metastases
Satwikananda *et al.* (21)	1	Male	56	3 m	NA	Staghorn	RNU	RCC	NA
He *et al.* (5)	5	Male	80	3 w	Yes	Multiple	Renal artery embolization	RCC	NA
		Male	60	2 m	NA	Multiple	Renal artery embolization	RCC	42 m, until FTD
		Male	58	20 y	NA	NA	Give up treatment	NA	FTD
		Male	53	3 m	NA	NA	RNU	RCC	33 m, until FTD
		Female	70	5 y	NA	Multiple	Conservation treatment	RCC	11 m, until FTD

y, years; UTI, urinary tract infection; NA, not available; RNU, radical nephroureterectomy; SCC, squamous cell carcinoma; UC, urothelial carcinoma; PCNL, percutaneous nephrolithotomy; FTD, follow-up termination date; w, weeks; m, months; ECIRS, endoscopic combined intrarenal surge; RCC, renal cell carcinoma.

by biopsy, including mucosal hydropathy lesions, pedicled papillary masses, villous or polypoid masses, local mucosal lichenoid changes, and abnormal mucosal color at the kidney stone site. If the above mucosal changes are detected intraoperatively, the possibility of a tumor should be highly suspected, and a warning biopsy should be performed.

Once the mucosal biopsy indicates malignancy, renal pelvic carcinoma should be treated and diagnosed according to the guidelines. Simultaneously, comprehensive consideration should be given to various aspects, including the tumor risk stratification, physical condition, and renal function, and individualized treatment should be selected. In this study, eight patients had carcinoma of the renal pelvis; two underwent radical surgery, three underwent local electrocautery or laser ablation of the tumor, two underwent palliative renal artery embolization, and one underwent radical surgery for a renal artery embolism. Notably, one patient with low-grade urothelial carcinoma with focal high-grade components underwent renal-sparing surgery and survived for more than 10 years. Two patients with high-grade carcinomas underwent local electrocautery or laser ablation, and no recurrence was observed within one year of surgery. Li *et al.* (22) suggested that UC usually cannot be cured, and the 5-year survival rate is approximately 15%. Except for one case in our postoperative group that was lost to follow-up, the other seven patients survived, indicating that promptly using the PCNL technique for the early detection of abnormal mucosal biopsies from malignant tumors of the renal pelvis and selecting the appropriate operative method can achieve good prognoses. Because of the small sample size of this study, each treatment regimen's effectiveness is not truly represented, and results are only useful for clinical reference. This study had some limitations. First, this was a retrospective study, which was subject to selection bias. Second, the sample size of this study was limited, and some patients were lost to early follow-up; therefore, accurately determining the malignant transformation in various pathological conditions was impossible.

Conclusions

In conclusion, patient indicators should be comprehensively evaluated before PCNL. For patients aged >50 years with a history of kidney stones of >1 year, severe hydronephrosis, urinary tract infections, and multiple large stones, the intraoperative mucosal condition should be comprehensively and carefully observed. Once a mucosal abnormality is detected, an early warning biopsy should be performed. A warning-type biopsy can help identify patients with malignant tumors and provide timely treatment to improve their prognosis.

Acknowledgments

Funding: This study was supported by Peking University People's Hospital Research and Development Funds (No. RDY 2021-21), Beijing Health Technologies Promotion Program (No. BHTPP2022082), and Peking University People's Hospital Scientific Research Development Funds (No. RDE2023-11).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-91/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-91/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-91/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-91/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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking University People's Hospital (No. 2024PHB170-001). Informed consent was obtained from all participating patients.

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Cite this article as: Qiao J, Tian C, An L, Hong Y, Huang X, Liu J. Application of warning biopsies in percutaneous nephrolithotomy. Transl Androl Urol 2024;13(8):1455-1462. doi: 10.21037/tau-24-91

