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Original Article

Medium-term follow-up of clinically insignificant residual fragments after minimal invasive percutaneous nephrolithotomy: prognostic features and risk factors

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Abstract: Minimal invasive percutaneous nephrolithotomy (MPCNL) has been commonly used in removing urinary stones. However, the detrimental effects of clinically insignificant residual fragments (CIRF) after MPCNL have not been entirely clarified. This study is aimed at investigating the clinical outcomes of CIRF after MPCNL. From July 2004 to June 2010, 1862 cases of urolithiasis underwent MPCNL. 185 cases of CIRF were subsequently diagnosed using CT scanning and followed up. During follow-ups, medical history, physical examination, routine blood and urine tests, subjective symptoms were recorded. A multiple-variable Cox regression was performed to evaluate the prognostic significance of different factors for CIRF after MPCNL. Of 185 cases of CIRF followed up for 31.4 months on average, 58 cases (31.4%) suffered symptomatic episodes, including 30 cases of hematuresis, 21 cases of low urinary tract symptoms and 7 cases of hematuresis complicated with renal colic. The results of Cox regression showed that past history of extracorporeal shock wave lithotripsy (ESWL), CIRF size, hypercalcuria and CIRF located in ureteropelvic junction (UPJ) are independent risk factors for medium-term symptomatic episodes of CIRF after MPCNL. We suggest that regular follow-ups should be considered for patients with CIRFs after MPCNL for timely treatments, especially for those who are hypercalcuria-complicated, have history of ESWL, or suffer relatively large CIRFs located in the UPJ.

Keywords: Minimal invasive percutaneous nephrolithotomy, clinically insignificant residual fragments, prognostic features

Introduction

Although urinary stones can be removed using a number of modalities, clinically insignificant residual fragments (CIRFs) are sometimes an unavoidable problem [1-4]. CIRFs are usually defined as residual fragments of urinary stones with a maximum diameter of ≤4 mm and an anatomically normal, uninfected and unobstructed upper urinary tract [5-7]. Are these CIRFs actually clinically insignificant? As a matter of fact, there have been a great amount of debates on the optimal treatment of these small and asymptomatic fragments of urinary stones. Several reports have demonstrated that CIRFs contribute much to the recurrence of urinary stones and should be regularly followed [8, 9], whereas several reports claimed that it is necessary to remove all the residual fragments to achieve a stone-free status [10, 11]. On the contrary, it is also suggested that small and asymptomatic residual fragments (no more than 4 mm) can be left in situ since spontaneous passage is very likely [7]. Uniform clinical programs have not been proposed for the management of CIRFs due to the disunity between research results.

It must be pointed out that the aforementioned reports are focused on CIRFs after extracorporeal shock wave lithotripsy (ESWL). In recent years, the long term efficacy and safety of ESWL has been questioned since it can give rise to the risk of recurrence, metabolic and anatomical abnormalities [12, 13]. Actually, before the introduction of ESWL, which has been commonly used in removing upper urinary tract calculi, even small-sized residual fragments were con-

Table 1. General and medical information of CIRF cases: univariable survival analysis

Index	Cases	Mean asymp. time (m)	Event	*P*
Number of patients	185	32.1±0.5	58	-
Age				0.345
<65 yr	100	32.8±0.7	29	
≥65 yr	85	31.3±0.9	29	
Gender				0.789
Male	98	32.1±0.7	32	
Female	87	32.2±0.8	26	
History of ESWL				<0.001
Yes	69	34.4±0.5	42	
No	116	28.4±1.1	16	
CIRF size (mm)				<0.001
<3.0 mm	93	34.6±0.5	12	
≥3.0 mm	92	29.7±0.9	46	
Hyperlipidemia				0.229
Yes	64	31.7±0.6	24	
No	121	32.4±1.0	34	
hypercalcuria				<0.001
Yes	74	29.0±1.0	40	
No	111	34.2±0.5	18	
Hyperuraecemia				0.067
Yes	61	30.2±1.1	24	
No	124	33.1±0.6	34	
Location of CIRF				<0.001
Upper renal calyces	50	34.6±0.7	4	
Middle renal calyces	22	35.9±0.2	2	
Lower renal calyces	62	34.6±0.5	7	
UPJ	51	25.2±1.2	45	

sidered to be a sign of unsuccessful surgical treatment of urinary stones [14]. The term "CIRF" is derived from early ESWL-related reports, and might be inappropriate to be considered to be an acceptable surgical outcome of MPCNL [15]. Recent reports have also shed some light on the prognosis of residual fragments after MPCNL, which is considered to have a higher stone-free rate than ESWL [15-17]. However, these reports are focused on the protective and risk factors for symptomatic episodes of residual fragments at all sizes. Our study is aiming to evaluate the risk factors for CIRF-induced recurrence of urinary stones using a survival analysis-based method.

Patients and methods

The clinical records of 1862 cases of urolithiasis treated MPCNL at our department between July 2004 and June 2010 were retrospectively reviewed. 185 cases of CIRF after MPCNL were selected for further analysis. The inclusion criteria were: 1) no clinical manifestations of active urinary stones after MPCNL; 2) small residual fragments (no more than 4 mm) detected using CT; 3) regular follow-ups after hospital discharge. The exclusion criteria were: 1) previous surgical history of urinary tract; 2) past history of bacterial nephritis or acute kidney injuries; 3) malignant tumors or other life-threatening co-morbidities. This study was approved by the Institutional Review Board of the General Hospital of Shenyang Military Area Command and met the criteria of waiving informed consent.

Preoperatively, non-contrast computed tomography (CT) and ultrasonography were used to confirm the location and size of stones; the stone size was measured as the maximum diameter. The patients with sterile urine were administered with broad spectrum prophylactic antibiotics to achieve an infection free state before surgical management. The patients underwent MPCNL in accordance to the guidelines and techniques in our hospital. 3 days after surgical treatment, the patients underwent CT scanning. CIRF was defined as non-infectious and non-obstructive residual fragments no more than 4 mm in maximum diameter, without anatomical abnormalities in kidneys. A stone-free state was defined as no detectable residual fragments and no evidence of infected or obstructed urinary tract. After hospital discharge, cases of CIRFs are regularly followed up. During follow-ups, medical history, physical examination, routine blood and urine tests, subjective symptoms were recorded.

Statistical analysis

Cox regression was performed to clarify the influence factors for symptomatic episodes of CIRF after MPCNL. The variables presenting

Table 2. Cox regression for medium-term symptomatic episodes of CIRF

Independent factors	OR	95% CI	*P*
History of ESWL	2.525	1.346-4.737	0.004
CIRF size	3.940	2.109-7.362	<0.001
hypercalcuria	2.688	1.498-4.824	0.001
CIRF located in UPJ	3.056	1.734-5.385	<0.001
Age	0.916	0.846-1.537	0.240
Hyperlipidemia	1.495	0.886-2.521	0.132
Hyperuraecemia	1.510	0.895-2.547	0.120

with $P<0.6$ in univariable survival analysis were involved in the final model and all categorical variables were transformed into dummy variables. A forward method with the likelihood ratio for covariate entry was used. $P<0.05$ was considered statistically significant.

Results

The 185 cases of CIRF were followed up at a median of 36 months; 58 cases (31.4%) suffered symptomatic episodes, including 30 cases of hematuresis, 21 cases of low urinary tract symptoms and 7 cases of hematuresis complicated with renal colic. Of the 58 cases suffering subjective symptoms, 52 presented with urinary stones more than 4 mm in maximum diameter and received ureteroscopic lithotripsy (URSL) while 6 presented with renal colic in UPJ and CIRF less than 4 mm were administered with spasmolysants. The 52 surgically treated cases all achieved a stone-free status after URSL while the 6 conservatively treated cases underwent spontaneous passages.

Of the 58 cases suffering subjective symptoms, 45 (77.6%) presented CIRFs in the UPJ, 4 (6.9%) in the upper renal calyces, 2 (3.4%) in the middle renal calyces and 7 (12.1%) in the lower renal calyces. The mean age of the 58 cases was (61.6±16.2) years and the mean size of CIRFs at hospital discharge was (3.4±0.5) mm. The mean asymptomatic time of the 185 cases of CIRF was (32.1±0.5) months and those of subgroups were presented in the **Table 1**.

Age, History of ESWL, CIRF size at hospital discharge, hyperlipidemia, hypercalcuria, hyperuraecemia and location of CIRF were involved in the final model. The results of Cox regression showed that age, hyperlipidemia, hyperuraecemia, past history of ESWL, CIRF size, hypercalcuria and CIRF located in ureteropelvic junction (UPJ) are independent risk factors for medium-term symptomatic episodes of CIRF after MPCNL (**Table 2**).

Discussion

Urolithiasis has become the third commonest clinical problem in urology, just next to urinary tract infection and prostate disorders, with a worldwide prevalence of 1-5% [18-21]. In recent years, a number of advanced therapeutic methods have been used in removal of urinary stones, such as ESWL, URSL and MPCNL. Open surgery is no longer a favorable choice except for some complex urinary stones. However, newly developed therapeutic methods, especially ESWL, are unavoidably associated with some asymptomatic residual fragments of urinary stones, which are usually considered to be clinically insignificant [14, 15]. These residual fragments named CIRFs are not always treated seriously.

Candau et al. [22] demonstrated that increasing stone burden necessitated secondary procedure in 37% of the patients with CIRFs after ESWL during a median of 40 months of follow-ups. Khaitan et al. [11] suggested that CIRFs after ESWL could re-grew in 59% of patients followed up to 60 months. As for surgical procedures, Raman et al. [17] demonstrated that 18 (42.9%) out of 42 patients with residual fragments after PCNL suffered stone-related events at a median of 32 months. Ganpule et al. [16] suggested that 84 (44.9%) out of 187 patients with residual fragments after PCNL underwent spontaneous passage at a mean follow-up of 24 months. Our study is focused on CIRFs after MPCNL, which are more likely to be left in situ after surgical procedures, and our data showed that 58 (31.4%) out of 185 cases of CIRF presented with subjective symptoms at a median of 36 months of follow-ups, which is lower than that reported by Raman et al. [17]; this may be because that it requires more time for CIRFs to grow into symptomatic stones, in comparison with residual fragments at all sizes.

ESWL has been used as a first-line therapeutic method in treating urinary stones. However, ESWL does also cause some damage on the kidney and ureter. Rassweiler [23] suggested that ESWL give rise to the risk of CIRF and that

this newly developed technology is not appropriate in treating the patients with renal stones more than 30 mm in maximum diameter. In addition, a recent report compared 207 cases of residual stones after ESWL and 175 cases of residual stones after PCNL and demonstrated that residual stones after ESWL are more likely to re-grow [24]. Our data showed that the patients with CIRFs after MPCNL, who had medical history of ESWL, are more likely to suffer growing residual fragments and subjective symptoms in the medium term. Since ESWL can cause functional damage and scars on kidneys, this group of patients might be less likely to undergo spontaneous passage of CIRFs after MPCNL.

Raman et al. [17] suggested that residual fragments after PCNL located in the UPJ are more likely to grow into symptomatic stones and that the location of residual fragments should be referred to as a conventional prognostic index. Our data showed that patients with CIRFs after MPCNL located in the UPJ are more likely to experience medium-term symptomatic episodes. This may be because that these small-size residual fragments are not always stably located in the UPJ, easily falling off and moving into the ureter. Raman et al. [17] also suggested that residual fragments more than 2 mm in maximum diameter are more likely to re-grow. Our data showed that bigger CIRFs are more likely to grow into symptomatic stones within a medium term. Ganpule et al. [16] demonstrated that hyperclcuria is a negative factor in spontaneous passage of residual fragments of urinary stones after PCNL. Our data also showed that patients with hypercalcuria are more likely to suffer asymptomatic episodes, which is probably due to calcium deposits in the urinary tract.

In existing reports, which are focused on residual fragments after PCNL at all sizes, past history of ESWL has hardly been referred to as a risk factor of recurrence in surgically treated patients [25]. Our study suggested that the patients that present with CIRFs after MPCNL and have history of ESWL should receive regular monitoring after hospital discharge. In addition, our study suggested that the CIRFs located in the UPJ are very likely to develop into symptomatic stones. The limitations of our study are as follows: 1) it is a one-center study; 2) long-term data were not obtained; 3) underdeveloped health consciousness in Chinese patients led to some loss to follow-ups. A multicenter large-scale study is needed to further investigate the risk factors for CIRF-related events after MPCNL.

Conclusion

As stated above, CIRFs after MPCNL are asymptomatic but not always "clinically insignificant" since a considerable proportion of them can grow into symptomatic stones. Regular after-discharge monitoring should be considered for patients with CIRFs after MPCNL, especially for those who are hypercalcuria-complicated, have history of ESWL, or suffer relatively large CIRFs located in the UPJ.

Disclosure of conflict of interest

None.

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References

[1] Ozgor F, Simsek A, Binbay M, Akman T, Kucuktopcu O, Sarilar O, Muslumanoglu AY and Berberoglu Y. Clinically insignificant residual fragments after flexible ureterorenoscopy: medium-term follow-up results. Urolithiasis 2014; 42: 533-538.

[2] Garg M, Singh V and Kumar A. Re: Osman et al.: clinically insignificant residual fragments: an acceptable term in the computed tomography era? (Urology 2013; 81: 723-726). Urology 2013; 82: 496-497.

[3] Mandal S, Singh V and Sankhwar S. Re: Osman et al.: clinically insignificant residual fragments: an acceptable term in the computed tomography era (Urology 2013; 81: 723-726). Urology 2013; 82: 493.

[4] Osman Y, Harraz AM, El-Nahas AR, Awad B, El-Tabey N, Shebel H, Shoma AM, Eraky I and El-Kenawy M. Clinically insignificant residual fragments: an acceptable term in the computed tomography era. Urology 2013; 81: 723-726.

[5] Delvecchio FC and Preminger GM. Management of residual stones. Urol Clin North Am 2000; 27: 347-354.

[6] Tan YH and Wong M. How significant are clinically insignificant residual fragments following lithotripsy? Curr Opin Urol 2005; 15: 127-131.

[7] Osman MM, Alfano Y, Kamp S, Haecker A, Alken P, Michel MS and Knoll T. 5-year-follow-

up of patients with clinically insignificant residual fragments after extracorporeal shockwave lithotripsy. Eur Urol 2005; 47: 860-864.
[8] El-Nahas AR, El-Assmy AM, Madbouly K and Sheir KZ. Predictors of clinical significance of residual fragments after extracorporeal shockwave lithotripsy for renal stones. J Endourol 2006; 20: 870-874.
[9] Fine JK, Pak CY and Preminger GM. Effect of medical management and residual fragments on recurrent stone formation following shock wave lithotripsy. J Urol 1995; 153: 27-32; discussion 32-23.
[10] Streem SB, Yost A and Mascha E. Clinical implications of clinically insignificant store fragments after extracorporeal shock wave lithotripsy. J Urol 1996; 155: 1186-1190.
[11] Khaitan A, Gupta NP, Hemal AK, Dogra PN, Seth A and Aron M. Post-ESWL, clinically insignificant residual stones: reality or myth? Urology 2002; 59: 20-24.
[12] Samad L, Aquil S and Zaidi Z. Paediatric percutaneous nephrolithotomy: setting new frontiers. BJU Int 2006; 97: 359-363.
[13] Guven S, Frattini A, Onal B, Desai M, Montanari E, Kums J, Garofalo M and de la Rosette J. Percutaneous nephrolithotomy in children in different age groups: data from the Clinical Research Office of the Endourological Society (CROES) Percutaneous Nephrolithotomy Global Study. BJU Int 2013; 111: 148-156.
[14] Moon YT and Kim SC. Fate of clinically insignificant residual fragments after extracorporeal shock wave lithotripsy with EDAP LT-01 lithotripter. J Endourol 1993; 7: 453-456.
[15] Raman JD, Bagrodia A, Bensalah K, Pearle MS and Lotan Y. Residual fragments after percutaneous nephrolithotomy: cost comparison of immediate second look flexible nephroscopy versus expectant management. J Urol 2010; 183: 188-193.
[16] Ganpule A and Desai M. Fate of residual stones after percutaneous nephrolithotomy: a critical analysis. J Endourol 2009; 23: 399-403.
[17] Raman JD, Bagrodia A, Gupta A, Bensalah K, Cadeddu JA, Lotan Y and Pearle MS. Natural history of residual fragments following percutaneous nephrostolithotomy. J Urol 2009; 181: 1163-1168.
[18] Ramello A, Vitale C and Marangella M. Epidemiology of nephrolithiasis. J Nephrol 2000; 13 Suppl 3: S45-50.
[19] Lee YH, Huang WC, Tsai JY, Lu CM, Chen WC, Lee MH, Hsu HS, Huang JK and Chang LS. Epidemiological studies on the prevalence of upper urinary calculi in Taiwan. Urol Int 2002; 68: 172-177.
[20] Bartoletti R, Cai T, Mondaini N, Melone F, Travaglini F, Carini M and Rizzo M. Epidemiology and risk factors in urolithiasis. Urol Int 2007; 79 Suppl 1: 3-7.
[21] Ketabchi AA and Aziziolahi GA. Prevalence of symptomatic urinary calculi in Kerman, Iran. Urol J 2008; 5: 156-160.
[22] Candau C, Saussine C, Lang H, Roy C, Faure F and Jacqmin D. Natural history of residual renal stone fragments after ESWL. Eur Urol 2000; 37: 18-22.
[23] Rassweiler JJ, Renner C, Chaussy C and Thuroff S. Treatment of renal stones by extracorporeal shockwave lithotripsy: an update. Eur Urol 2001; 39: 187-199.
[24] Chongruksut W, Lojanapiwat B, Tawichasri C, Paichitvichean S, Euathrongchit J, Ayudhya VC and Patumanond J. Kidney stones recurrence and regrowth after extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy. J Med Assoc Thai 2011; 94: 1077-1083.
[25] Choo MS, Jeong CW, Jung JH, Lee SB, Jeong H, Son H, Kim HH, Oh SJ and Cho SY. External validation and evaluation of reliability and validity of the S-ReSC scoring system to predict stone-free status after percutaneous nephrolithotomy. PLoS One 2014; 9: e83628.