



Stone composition independently predicts stone size in 18,029 spontaneously passed stones

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Abstract

Purpose To evaluate whether the size of spontaneously passed stones (SPS) may be associated with clinical parameters.

Methods A search for SPS was conducted in our electronic stone database, comprising data on stones analyzed over the last 33 years at our institution. Adults with upper urinary tract stones were included. Cases with stenotic urinary tract disease or past history of anastomotic urinary tract surgery were excluded. Stone size expressed as maximal stone diameter (MSD) and stone volume (SV) was compared between groups by one-way ANOVA. Logistic regression analyses were performed to identify predictors of MSD ≥ 6 mm.

Results Overall mean MSD and SV for 18,029 SPS was 4.1 mm and 11.5 mm³, respectively, and significantly differed between stone composition groups ($p < 0.001$). The lowest mean MSD and SV were found for calcium oxalate monohydrate (3.6 mm and 9.0 mm³, respectively) and the highest mean MSD and SV were found for struvite (7.9 mm and 61.0 mm³, respectively). Stone composition and increasing age were found to be independent predictors of MSD ≥ 6 mm (both $p < 0.001$). Sex differentiation did not contribute as a predictor of MSD ≥ 6 mm.

Conclusions Stone composition and—to a lesser extent—age serve as independent predictors of size of spontaneously passed stones. Of particular importance, large spontaneously passed stones of ≥ 6 mm may be frequently found in cystine, brushite or struvite stone formers, whereas a minority of all calcium oxalate stones exceed that cutoff. Future studies shall evaluate these parameters as possible predictors of spontaneous stone passage.

Keywords Urinary stone · Stone size · Stone composition · Spontaneous passage · Age · Recommendations · Adults

Introduction

Urinary stone disease is a widespread medical condition with an annual incidence of symptomatic stone events of 0.1–0.4% and a recurrence rate of $> 50\%$ within 10 years [1]. It is estimated that 64–78% of ureteral stones are spontaneously expelled [2, 3]. The remaining stones are either fragmented by extracorporeal shockwave lithotripsy or actively

withdrawn by endourological techniques such as ureteroscopy and percutaneous nephrolithotomy.

The probability for spontaneous passage of ureteral stones follows an almost linear relationship with stone size [4, 5]. Based on a computed tomography (CT) study, spontaneous stone passage rates were 78, 60 and 39% for stones < 5 mm, 5–7 mm and > 8 mm, respectively [6]. Stone size has also been associated with time to spontaneous stone passage, resulting in an average of 8, 12 and 22 days for passage of ureteral stones of 2, 3 and 4–6 mm, respectively [7]. This relationship forms the rationale for international guidelines recommending conservative treatment based on maximal stone diameter (MSD) [8–10]. Another predictor of spontaneous stone passage is stone location at diagnosis, with passage rates of 45–75%, 22–60% and 12–48% for distal, mid and proximal ureter stones, respectively [4, 6]. Individual characteristics such as persistent pain, renal insufficiency,

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signs of infection and comorbidities should also be considered in treatment decision.

Altogether, only sparse data regarding spontaneous stone passage according to stone size are available to date [11]. Particularly, only few studies to date have considered the relationship between the size of spontaneously passed stones (SPS) and patient or stone clinical factors such as age, sex and stone composition [7, 12, 13]. Further evaluation of these parameters could provide novel insights that may ultimately impact on recommendations for conservative stone treatment.

In the present study, a search for predictors of size of SPS was conducted in our stone database, including a differentiation for the eight most common stone compositions.

Patients and methods

Study design

A search for SPS was conducted in our electronic stone database in May 2018. This database was built over the last 33 years at our institution (1985–2018) in Paris. It contains data on clinical, morphological and constitutional characteristics of stones originating from France. Patient data were provided by the referring clinician and stone analysis was performed at our institution. Only stones for which no operative treatment was necessary were coded as SPS. All SPS originating from adults and labeled as upper urinary tract stones at the time of diagnosis were considered for this study. Cases with documented stenotic urinary tract disease or with past history of anastomotic urinary tract surgery were excluded. Age and sex were retrieved for each case. Stones were classified according to a methodology previously described by M.D. [14]. This included the analysis of various parts of each stone for determination of the main crystalline constituent (≥ 50 –100% of total constituent). Stone constituents were ordered after the Daudon classification, from which the eight most frequent main crystalline constituents (thereafter called stone composition) were selected for analysis: calcium oxalate monohydrate (COM), calcium oxalate dihydrate (COD), anhydrous uric acid (UA0), uric acid dihydrate (UA2), carapatite (CA), struvite (STR), brushite (BR) and cystine (CYS) [15].

Outcomes

Primary outcome was stone size, as measured by maximal stone diameter (MSD) and stone volume (SV). Stone volume was calculated by the formula of an ellipsoid: $4/3 \times \text{Pi} \times A \times B \times C$, where A, B and C corresponded to maximal stone radii in three dimensions, respectively. All measurements were done on tangible stones using a metric

caliper. Whenever more than two SPS were available per case, the characteristics of the SPS with the largest MSD were considered. Substrates for stone size were generated using an MSD cutoff of 6 mm to address predictors for stones that are not considered to have a high likelihood of spontaneous passage according to the current guidelines of the European Association of Urology (EAU) [8].

Statistical analysis

The primary outcome as well as other continuous variables was analyzed using Pearson's correlation coefficient, Student's *t* test and one-way ANOVA with Tukey post hoc comparisons, as appropriate. For stone volume, geometric mean values were reported. Logistic regression analyses were performed to identify predictors of $\text{MSD} \geq 6$ mm. Association between categorical variables was evaluated by the Chi-square test or Fischer's exact test, as appropriate. All statistical tests were two-sided and *p* values < 0.05 were considered significant. Statistical analysis and graph plotting were performed with IBM SPSS Statistics 24.0 (IBM Corp., Armond, NY, USA).

Results

From 80,253 stones listed in the database, a total of 19,139 were labeled as SPS and 18,029 were available for analysis (Supplementary Fig. 1). Patient and stone characteristics are summarized in Table 1, including a stratification for stone composition. Overall mean age was 45 years [standard deviation (SD) 14] and significantly differed between males (46 years, SD 14) and females (44 years, SD 15) ($p < 0.001$). Mean age also significantly differed over the stone composition groups ($p < 0.001$) (Table 1). The distribution of cases over age according to sex and stone composition is presented in Fig. 1a, b, respectively. The predominant stone composition was COM over all age groups. The proportion of COD stones decreased with age, whereas the proportions of UA0 and UA2 stones increased with age. The highest proportions of STR were found in the oldest age group, whereas the highest proportion for CYS was in the youngest age group. There was a majority of male cases over all stone composition categories, except for CA which included a majority of female cases (male/female ratio 0.88) and STR which included an equal number of male and female cases (ratio 1.00) (Table 1).

Comparisons for stone size

The mean overall MSD was 4.1 mm (SD 2.2) and mean overall SV was 11.5 mm^3 (SD 3.5). Increasing age significantly correlated with increase in MSD ($r = 0.15$, $p < 0.001$)

Table 1 Patient and stone characteristics with stratification for stone composition

Variable	Total	Stone composition ^a								P
		COM	COD	UA0	UA2	CA	STR	BR	CYS	
Cases, no. (%)	18,029 (100)	11,126 (61.7)	3405 (18.9)	1499 (8.3)	321 (1.8)	1362 (7.6)	54 (0.3)	156 (0.9)	106 (0.6)	–
Age, mean (SD), years	45 (14)	46 (13)	39 (13)	59 (13)	57 (13)	41 (14)	56 (19)	45 (15)	41 (17)	<0.001
Male/female ratio	3.01	3.03	5.09	3.93	4.73	0.88	1.00	4.20	1.94	<0.001
Maximal stone diameter, mean (SD) (mm)	4.1 (2.2)	3.6 (1.8)	4.5 (2.1)	5.5 (2.9)	4.6 (2.7)	4.9 (2.6)	7.9 (3.9)	6.2 (2.4)	6.8 (3.4)	<0.001
Stone volume, geometric mean (SD) (mm ³)	11.5 (3.5)	9.0 (3.1)	14.0 (3.4)	21.0 (4.0)	12.0 (4.4)	18.3 (3.9)	61.0 (4.5)	39.4 (3.1)	42.1 (3.7)	<0.001

COM Calcium oxalate monohydrate, COD calcium oxalate dihydrate, UA0 anhydrous uric acid, UA2 uric acid dihydrate, CA carapatite, STR struvite, BR brushite, CYS cystine, SD standard deviation

^aOrdered after the Daudon classification, considering the main crystalline constituent (≥ 50 –100% of total constituent) [15]

and increase in SV ($r=0.17$, $p<0.001$). Males showed significantly lower mean MSD and mean SV compared to females (4.0 mm versus 4.1 mm, $p=0.01$ and 11.2 mm³ versus 12.3 mm³, $p<0.001$, respectively).

Mean MSD differed significantly between stone composition categories ($p<0.001$) (Fig. 2a). The lowest mean MSD was found for COM (3.6 mm, 95% CI 3.5–3.6) and significantly differed from all other stone categories in a post hoc analysis: 4.5 mm for COD (95% CI 4.4–4.6), 5.5 mm for UA0 (95% CI 5.3–5.6), 4.6 mm for UA2 (95% CI 4.3–4.9), 4.9 mm for CA (95% CI 4.8–5.0), 7.9 mm for STR (95% CI 6.9–9.0), 6.2 mm for BR (95% CI 5.8–6.6) and 6.8 mm for CYS (95% CI 6.2–7.5) ($p<0.001$ for all).

Mean SV also differed significantly between stone composition categories ($p<0.001$) (Fig. 2b). The lowest mean SV was found for COM (9.0 mm³, 95% CI 8.8–9.2) and significantly differed from all other stone categories in a post hoc analysis: 14.0 mm³ for COD (95% CI 13.4–14.6), 21.0 mm³ for UA0 (95% CI 19.6–22.6), 12.0 mm³ for UA2 (95% CI 10.2–14.1), 18.3 mm³ for CA (95% CI 17.0–19.7), 61.0 mm³ for STR (95% CI 40.5–91.8), 39.4 mm³ for BR (95% CI 32.9–47.2) and 42.1 mm³ for CYS (95% CI 32.7–54.2) ($p\leq 0.001$ for all).

Comparisons considering a stone size cutoff

Out of the 18,029 stones available for analysis, 3166 (18%) had an MSD ≥ 6 mm. The proportion of stones with an MSD ≥ 6 mm significantly differed between stone composition groups ($p<0.001$): 10% for COM, followed by 25% for COD, 26% for UA2, 29% for CA, 38% for UA0, 53% for BR, 55% for CYS and 65% for STR (Supplementary Fig. 2). In a logistic regression analysis, age and stone composition were found to be independent predictors for SPS ≥ 6 mm (Table 2). For increments of 10 years of age, the adjusted odds ratio (OR) for SPS ≥ 6 mm was 1.37 (95% CI 1.33–1.41; $p<0.001$). As for stone composition, the adjusted OR for SPS ≥ 6 mm was lowest for UA2 (OR 2.5, 95% CI 1.9–3.2; $p<0.001$) and highest for STR (OR 17.1, 95% CI 9.1–32.4; $p<0.001$), respectively, when compared to COM.

Comparisons for age subgroups

A significant interaction was found between stone composition and age after the addition of multiplicative interaction terms in the multivariate logistic regression analysis for MSD ≥ 6 mm ($p<0.001$, data not shown). This prompted us to verify whether the distribution of stones ≥ 6 mm over age groups would vary according to their stone composition. A significant association was found between stone size (cutoff 6 mm) and age (grouped by decades) for COM ($p<0.001$), COD ($p<0.001$), CA ($p<0.001$) and CYS ($p=0.017$), whereas no evidence for such association was found for UA0

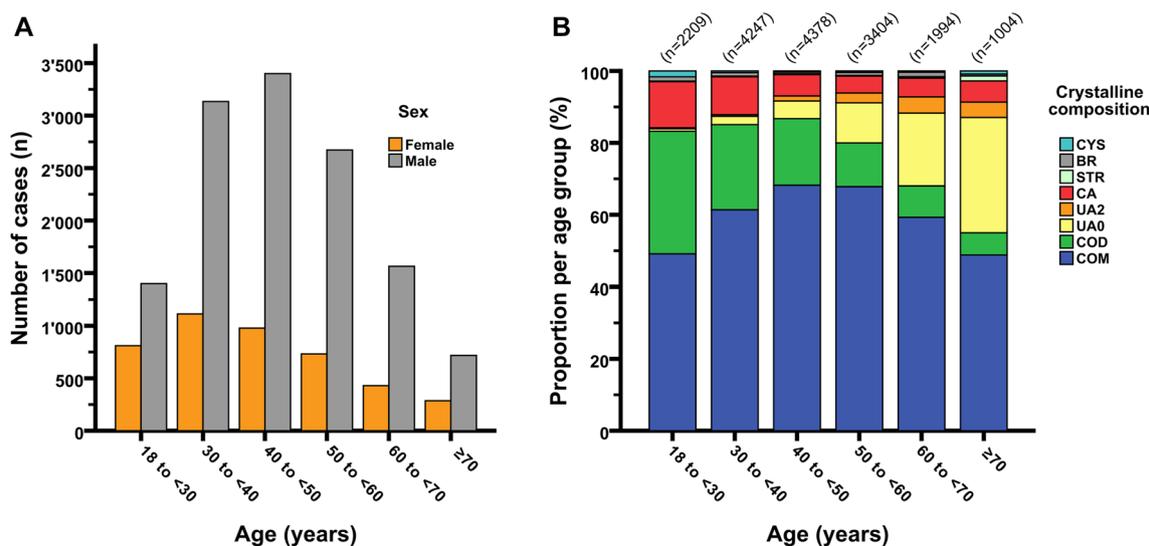


Fig. 1 Distribution of cases over age groups according to sex (a) and stone composition (b). *COM* Calcium oxalate monohydrate, *COD* calcium oxalate dihydrate, *UA0* anhydrous uric acid, *UA2* uric acid dihydrate, *CA* carapatite, *STR* struvite, *BR* brushite, *CYS* cystine

($p=0.14$), *UA2* ($p=0.33$), *STR* ($p=0.74$) and *BR* ($p=0.53$) (Supplementary Fig. 3).

Discussion

Stone size and stone location have been repeatedly reported as predictors of spontaneous stone passage in currently available literature [3–7, 16–19]. Remarkably, no prior study to date has evaluated the predictors of the size of SPS expressed as MSD and SV. In the present study, the characteristics of 18,029 SPS were analyzed and stone composition was found to be a major, independent predictor of stone size. Patients' age also contributed as an independent predictor of stone size, although with lower odds than stone composition. Sex differentiation did not contribute as a significant predictor of stone size.

Few studies on natural history of stone expulsion have detailed the overall mean MSD of SPS, which ranged between 5.4 and 6.3 mm [5, 12, 19]. In another study, only 47 out of 566 SPS (8%) were found to have an MSD ≥ 6 mm. In those studies, stone size measurements were based on plain radiographs or CT scans. The latter measurements are subject to inaccuracy and may not adequately reflect true stone size parameters [20]. In contrast, measurements were performed on tangible stones in this study, resulting in an overall mean MSD of 4.1 mm, with 18% of all SPS having an MSD ≥ 6 mm. Also, each stone was measured in three axes, resulting in an overall mean SV of 11.5 mm³. To the best of our knowledge, this is the first report on SPS including SV measurements.

In studies evaluating the natural history of conservatively managed ureteral stones, neither age nor sex contributed as a predictor of spontaneous passage [7, 18, 19]. Based on the current findings, the odds predicting an SPS ≥ 6 mm significantly increased by 1.37 for every increase in 10 years of age, whereas no association was found with sex. In subgroup analyses, the relationship between age and stone size was found to be particularly valid for *COM*, *COD*, *CA* and *CYS* stones. Of interest, the distribution of stone composition over age groups adhered to observations found in prior reports [2, 21]. *COM* stones were predominant in all age groups, whereas the proportion of *COD* stones decreased with age and *UA* stones increased with age.

Most importantly, significant size differences were found between stone compositions. Of all stone compositions, *COM* and *COD* stones showed the lowest mean MSD (3.6 mm and 4.5 mm, respectively) and the lowest and second-lowest mean SV (9.0 mm³ and 14.0 mm³, respectively). These two stone compositions accounted for the vast majority (81%) of all SPS, in accordance with current reports on overall stone prevalence in European countries [2]. Importantly, 90% of *COM* and 75% of *COD* stones had an MSD < 6 mm. Hence, a majority of all calcium oxalate stones fell within the current EAU guidelines on urolithiasis, which consider stones < 6 mm to have a high likelihood of spontaneous passage [8, 9]. Comparatively, more than a quarter of all *UA* stones and more than half of all *BR* and *CYS* stones surpassed the 6 mm cutoff. The largest stone size was found for *STR* stones (mean MSD 7.9 mm, mean SV 61 mm³). Because the latter stone type is typically associated with urinary tract infection [22], active stone removal should be considered irrespective of stone size. This

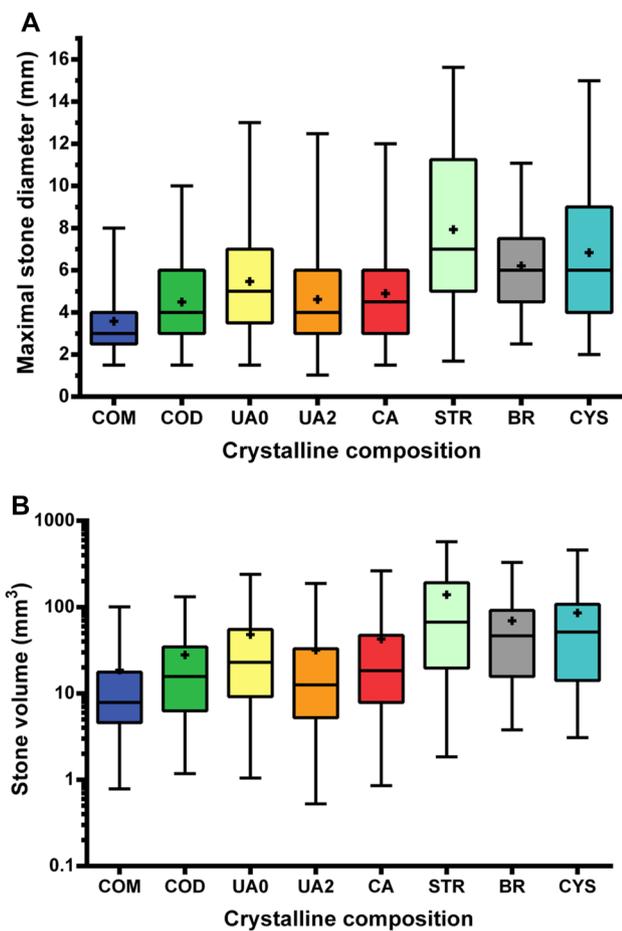


Fig. 2 Distribution of stone size parameters (maximal stone diameter in **a** and stone volume in **b**) over stone composition categories. Box plots are median (line), interquartile range (box) and 97.5th/2.5th percentiles (whiskers). Mean and geometric mean values are shown as “+” in A and B, respectively; *COM* calcium oxalate monohydrate; *COD* calcium oxalate dihydrate; *UA0* anhydrous uric acid; *UA2* uric acid dihydrate; *CA* carapatite; *STR* struvite; *BR* brushite; *CYS* cystine

may well explain why only a low number of spontaneously passed STR stones was found in our stone database.

Two distinct scenarios or the combination thereof may explain the association of age and stone composition with size of SPS. First, size differences may be attributable to relative stone growth rate, which may be higher in older patients as a consequence of reduced thirst and fluid intake [23], and which may differ between stone compositions. Consequently, at a constant probability of stone displacement from kidneys toward the ureters, the probability for a larger stone to reach the ureters would be higher in case of rapid stone growth. Accordingly, relative stone growth rate would be highest for CYS, BR and STR, which were also found to have the lowest rate of spontaneous expulsion in a previous evaluation based on our stone database, thus supporting this first hypothesis [2]. Second, size differences

Table 2 Logistic regression analysis to predict maximal stone diameter ≥ 6 mm

Variable	Univariable		Multivariable ^b	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Stone composition^a				
COM	1.0 (Ref.)		1.0 (Ref.)	
COD	3.1 (2.8–3.4)	<0.001	3.9 (3.5–4.3)	<0.001
UA0	5.6 (4.9–6.3)	<0.001	3.8 (3.4–4.4)	<0.001
UA2	3.3 (2.6–4.3)	<0.001	2.5 (1.9–3.2)	<0.001
CA	3.7 (3.2–4.2)	<0.001	4.6 (4.0–5.3)	<0.001
STR	16.9 (9.6–29.6)	<0.001	17.1 (9.1–32.4)	<0.001
BR	10.2 (7.4–14)	<0.001	11.6 (8.3–16.3)	<0.001
CYS	11.1 (7.5–16.3)	<0.001	13.7 (9.0–20.7)	<0.001
Age (continuous, decades)	1.33 (1.30–1.37)	<0.001	1.37 (1.33–1.41)	<0.001
Sex				
Male	1.0 (Ref.)		1.0 (Ref.)	
Female	0.92 (0.84–1.01)	0.08	0.93 (0.84–1.02)	0.14

OR odds ratio, *95% CI* 95% confidence interval, *COM* calcium oxalate monohydrate, *COD* calcium oxalate dihydrate, *UA0* anhydrous uric acid, *UA2* uric acid dihydrate, *CA* carapatite, *STR* struvite, *BR* brushite, *CYS* cystine

^aOrdered after the Daudon classification, considering the main crystalline constituent (≥ 50 –100% of total constituent) [15]

^bIncluding all variables shown in the table

may be attributable to anatomical differences, with larger ureters in stone formers with high recurrence rate as a consequence of repeated ureteral obstruction and dilation. Of interest, stone composition has recently been linked with stone recurrence, with a minority of COM and COD as well as a majority of BRU and CYS presenting as recurrent stone formers, respectively, thus matching this second hypothesis with our results [24].

Three stone compositions deserve particular attention, because their composition may be predicted based on clinical parameters and patients’ past history. First, UA stones have been associated with metabolic syndrome, are radio-lucent, have a low Hounsfield count on CT imaging and typically occur in the older population, as confirmed in this study [21, 25, 26]. Second, BR stones have been associated with hypercalciuria and hyperparathyroidism, and have been repeatedly showed to have the highest mean Hounsfield count on CT imaging [22, 26–29]. Third, CYS stones can easily be predicted whenever cystinuria has been readily diagnosed. Considering the above, it could be that a larger stone size cutoff for conservative treatment may be considered whenever UA, BR or CYS stones are suspected.

A limitation to this study was the lack of data which would have allowed calculation of the rate of spontaneous stone passage and the predictors thereof. This would

necessitate the observation of newly diagnosed patients over time and must be addressed in future studies. Time from diagnosis to passage was not known and may account as a confounder, since time accorded for conservative treatment may be associated with age due to concern with surgery. Several other parameters were not available for analysis and may have contributed as cofounders: history of prior stone passage or stone surgery, medical expulsive therapy, proportion of SPS retrieved for analysis and stone alterations during expulsion or collection. Despite these limitations, the strength of this study is the considerable number of SPS, which arguably may mitigate the impact that cofounders might have had on the results. This study might simulate future research to develop a more personalized treatment plan and follow-up for recurrent stone formers based on their age and stone composition.

Conclusions

Stone composition is a strong and independent predictor of the size of SPS. A minority of all COM and COD stones surpass 6 mm in maximal diameter, whereas a majority of BR, CYS and STR stones exceed that cutoff. To a lesser extent, age also serves as an independent predictor of stone size of SPS. Future studies shall evaluate these parameters as possible predictors of spontaneous stone passage.

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Author contribution EXK: protocol/project development, data analysis and manuscript writing/editing; VDC: protocol/project development, data analysis and manuscript writing/editing; MA: manuscript writing/editing; SD: data analysis and manuscript writing/editing; MD: protocol/project development, data collection or management, data analysis and manuscript writing/editing; OT: protocol/project development, data analysis and manuscript writing/editing.

Compliance with ethical standards

Conflict of interest Olivier Traxer is a consultant for Coloplast, Rocamed, Olympus, EMS and Boston Scientific. Steeve Doizi is a consultant for Coloplast. Etienne Xavier Keller is supported by a Travel Grant from the University Hospital Zurich and from the Kurt and Senta Herrmann Foundation. Vincent De Coninck is supported by the EUSP scholarship from the European Association of Urology and by a grant from the Belgische Vereniging voor Urologie (BVU).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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