Risk Factors for Ureteral Damage in Ureteroscopic stone Treatment: Results of the German Prospective Multicentre Benchmarks of Ureterorenoscopic Stone Treatment—Results in Terms of Complications, Quality of Life, and Stone-Free Rates Project

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\textbf{Keywords}  
Nephrolithiasis · Urolithiasis · Ureteroscopy · Ureteral damage · Post-ureteroscopic lesion scale

\textbf{Abstract}  
\textbf{Background:} The Post-Ureteroscopic Lesion Scale (PULS) is a validated, standardised scale that classifies iatrogenic ureteral lesions during ureteroscopy (URS). \textbf{Objective:} To determine risk factors for the various PULS-grades caused by URS. \textbf{Method:} We prospectively investigated the independent influence of various risk factors in correlation with PULS-Grade 1+ and 2+ on 307 patients with ureterorenoscopic stone treatment from 14 German urologic departments. \textbf{Results:} The following are the outcomes of the study: 117 (38.4\%) and 188 (61.6\%) of the calculi (median stone size 6 mm) were found in the kidney or ureter; 70\% and 82.4\% underwent preoperative or postoperative ureteral stenting; 44.3\% and 7.2\% received laser or ballistic lithotripsy; 60\% of the patients presented with PULS grade 1+ and 8\% with PULS grade of 2+. Only intracorporal lithotripsy revealed a significant independent risk factor for PULS grade 1+ or 2+. Both laser and ballistic therapies raised the probability of PULS grade 1+ by the factors 3.6 ($p = 0.001$) and 3.9 ($p = 0.021$), respectively. The ORs in conjunction with PULS grade 2+ were 3.1 ($p = 0.038$) and 5.8 ($p = 0.014$) respectively. Neither endpoint exhibited a significant difference regarding the lithotripsic procedure (laser vs. ballistic). \textbf{Conclusion:} Intracorporeal lithotripsy is associated with a significant increase in damage to the ureter; further research is needed to determine its long-term effects.

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Introduction

Complete stone clearance and low therapy-associated morbidity are considered the optimal outcomes when treating urolithiasis by retrograde intrarenal surgery [1, 2]. Thanks to extensive improvements in the endoscopic technology (smaller diameter, better visualisation), as well as lithotriptors and other assisting devices (guide wires, stone-capturing baskets), the role of ureteroscopy (URS) has grown dramatically in recent years and is now considered the standard therapy for stones measuring ≤2 cm in the upper urinary tract (UT) [3]. URS is much more effective and reveals lower re-intervention rates than extracorporeal shock-wave lithotripsy; however, it correlates with more therapy-associated morbidity and higher probability for the peri-interventional placement of a ureteral stent [1].

Schoenthaler et al. [4] introduced the Post-Ureteroscopic Lesion Scale (PULS; Fig. 1) in 2012 – the empirically developed standardised classification of intraoperative ureteral lesions following URS whose aim it is to help standardise the postoperative placement of a ureteral stent. The same working group published robust interrater reliability (Kendall’s W = 0.69, p < 0.001) between URS-experienced endourologists and trainees (n = 20 and n = 17) evaluating 100 standardised video sequences [5].

The prospective multicentric Benchmarks of ureterorenoscopic stone treatment-results in terms of complications, quality of life, and stone-free rates trial (BUSTER) was carried out at 14 German urologic departments in 2015. The working group leading this study had already demonstrated that ad 1: as a daily routine intervention at German urology departments, URS is a safe and effective procedure to treat urinary stones in the upper UT, that ad 2: the preoperative and postoperative placement of a ureteric stent is a well-established intervention, and that ad 3: PULS constitutes a standardised classification for intraoperative ureteral lesion assessment following URS that reveals high interrater reliability, even between physicians and nursing staff [6]. The most recent literature yields no data proving that preoperative ureteral stenting is associated with a significantly lower probability of intraoperative ureteral lesions (according to the PULS). Neither is there any solid evidence that stone disintegration is associated with serious damage to the ureter, nor of any related differences among various technologies for intracorporal lithotripsy. It was therefore the aim of this BUSTER investigation to analyse the risk factors for

Materials and Methods

Trial Criteria and Data Collection

The BUSTER study aimed to collect prospective data on patients who have undergone stone-related URS therapy at 14 German urology departments. The trial has been granted Ethics-Committee approval (AS 136[bB]/2014, Ethics Committee of the Regional Medical Association Brandenburg) and was registered in the German Registry of Clinical Studies (DRKS-ID: DRKS00007668) [7]. Between January and April 2015, patients at the participating institutions who had undergone URS due to UT urolithiasis were asked to participate in the study, and those who consented and were able to fill in a brief quality-of-life questionnaire (Health-Survey short form-8) on postoperative day 30, and to return the questionnaire. A series of patient-related and therapy-associated criteria were assessed according to the study protocol [7]. The decision as to the patient’s indication regarding postoperative ureteral stenting and which equipment to employ was the individual surgeon’s mostly corresponding to particular treatment standards of each centre.

Prior to trial initiation, the participating surgeons were instructed on how to apply the PULS classification [4, 5]. Every operating room was outfitted with a laminated chart containing graphics illustrating the 6 PULS grades (0–5; Fig. 1). At the end of the operation, the patient’s upper UT was examined endoscopically and retrograde contrast medium used to determine the PULS grade in the upper UT.

The following study criteria were applied in this trial: patient age (continuous in years), gender, body mass index (continuous in kg/m²), American Society of Anesthesiologists-Score (dichotomised in 3+ vs. 1–2), hospital volume (number of URS performed per clinic in 2015), physician’s qualification level (classified as assisting physician vs. 0–5 years as a consultant vs. >5 years as a consultant), pre-URS stenting, stone location, number of stones (solitary vs. multiple), stone size (continuous in mm), surgical indication (elective vs. acute), type of instrument (flexible ± semirigid vs. semirigid only), type of disintegration (none vs. laser vs. ballistic).

Statistical Analysis

Our variables are indicated as the median and within the interquartile range (IQR). Fisher’s Exact Test was applied to assess the distribution of categorical variables.

We constructed univariate models and 2 multivariate logistic regressions models to calculate the influence of various variables on our 2 binary endpoints (1): PULS 1+ (vs. PULS 0) and (2): PULS 2+ (vs. PULS 0–1). The influence of predictive variables on both endpoints was assessed via the OR including the 95% CI. As the event rate was low, the multivariate model for endpoint PULS 2+ was reduced (≥8 events per variable influence are required) [8, 9]. Internal validity of our variables in the various MLRM was tested via the bootstrap technique using 1,000 samples, and thus our p values are bootstrap-corrected.

Our data analysis relied on SPSS 24.0 (IBM Corp. Released 2016, IBM SPSS Statistics for Windows, Version 24.0; Armonk, NY, USA). All our p values are bilateral, and we set the level of statistical significance for all tests at p < 0.05.
Results

Descriptive Analysis of Trial Criteria

Of the 307 patients who had undergone unilateral URS stone therapy enrolled in the BUSTER study, 201 (65.5%) were male. Of the 14 centres participating in this study each enrolled from 6 to 59 patients, and the median number of URS stone treatments per clinic in 2015 was 144 (IQR 109–208). The patients’ median age was 54.4 years (IQR 44.4–65.8) and the median body mass index 27.5 kg/m² (IQR 24.4–31) respectively. In all, 79.9% of the patients presented an American Society of Anesthesiologists score of 1 or 2.

Fig. 1. PULS grades 0–5 with the assessments of iatrogenically-triggered ureteral lesions after URS [4]. Grade 0 = no lesion (a), Grade 1 = superficial mucosal lesion or significant mucosal oedema or haematoma (b), Grade 2 = lesion extends into the submucosa or muscularis (c), Grade 3 = evidence of perforation affecting a maximum 50% of the ureteral circumference (d), Grade 4 = evidence of perforation covering more than 50% of the ureteral circumference (e), Grade 5 = complete tear in the ureter (f). These illustrations kindly provided by the authors (Schoenthaler). PULS, post-ureteroscopic lesion scale.
Two-hundred and fifteen patients (70%) underwent preoperative ureteral stenting; 230 (74.9%) received prophylactic antibiotic treatment perioperatively. The median operating time to perform URS was 35 min (IQR 23–55). The surgeons had a median 6.5 years of experience as urology specialists (IQR 1–14). Semirigid URS was carried out only in 198 patients (64.7%), while another 53 (17.3%) underwent semirigid URS in combination with a flexible device. Fifty-five patients (18%) underwent flexible URS exclusively, 42 of whom in conjunction with the use of an ureteral access sheath. Overall, 147 patients (47.9%) received no intracorporal lithotripsy; 136 (44.3%) patients underwent laserlithotripsy and 22 (7.2%) patients ballistic lithotripsy (with 2 patients undergoing various lithotripsy procedures during the same operation).

The median stone size of the index calculi measured 6 mm (IQR 4–8); 117 (38.4%) and 188 (61.6%) of them were detected in the kidney or ureter, respectively, 68 patients (22.1%) presented multiple concrements. 211 patients (68.7%) were completely stone-free after URS. 253 (82.4%) of all patients received ureteral post-stenting; stents were removed from 24.9% (63/253) of the patients during their hospital stay (within 2 days); another 157 patients’ stents (62.1%) were to remain in place for a maximum 14 days. Our surgeons’ assessments of the patients’ PULS grades were 0, 1, 2 and 3 in 40% (n = 122), 52.1% (n = 159), 6.9% (n = 21) and 1% (n = 3) respectively.

**Regression Analyses for Endpoint PULS 1+**
The univariate analysis of the influence of our study’s criteria on endpoint 1 (PULS 1+) revealed that only the stone size (continuous, in mm) and disintegration exerted a significant effect: each millimetre increase in the stone size raised the endpoint’s probability by 13.6% (95% CI 5.4–22.3%; p = 0.001; p [Bootstrap-corrected] = 0.002). ORs for disintegration via laser or ballistics were 4.13 (95% CI 1.54–12.59; p = 0.001; p [Bootstrap-corrected] = 0.005; reference: no stone disintegration).

In our reduced multivariate model for endpoint 2 (reduced to avoid potential overfitting considering only 24 events), which therefore consisted only of the 3 variables preoperative ureteral stenting, stone size, and disintegration, only the last predictor variable was significant. Laser or ballistic displayed ORs of 3.06 (p = 0.038) and 5.84 (p = 0.014; Table 2). We detected no significant difference between the type of lithotripsy (laser vs. ballistic) in influencing an endpoint (p = 0.307; p [Bootstrap-corrected] = 0.291). In the “lithotripsy” (laser or ballistic) and “no lithotripsy” groups, 11.5 and 4.1% of the patients exhibited endpoint PULS 2+ (p = 0.019) respectively.

**Discussion**
In our earlier BUSTER-trial research, we demonstrated the PULS scoring system’s high intrarater reliability (κ = 0.883, p < 0.001) in grading ureteral lesions on a daily routine basis in a multicentric setting following URS stone treatment [6]. As these results concur with other studies’ findings, PULS can justifiably be considered a reproducible grading system for ureteral lesions after URS [4, 5, 10, 11]. Being so very reliable, the PULS scoring system enables us to standardise the placement of postoperative ureteral stents. Schoenthaler et al. [4] recommend the following empirically tested procedure: PULS-Grad 0 requires no stent, and PULS grades 1, 2, 3 and 4 a postoperative stent in place for 2, 10–14, 21–28 or 42–56 days respectively. Although our cross-section study illustrating the daily routine applying the PULS staging system correlated significantly and positively with postoperative stent placement and its duration in place, we must admit that at present, not all clinicians are
applying consistently objective criteria on a daily basis (namely, those of the PULS scoring system’s creators) [6]. A total of 82.4% of our trial patients received a post-operative ureteral stent – even those who were postoperatively stone-free had a rate of 80.1%. Of the 94 patients in the BUSTER study who were stone-free and PULS grade 0, 65 (69.1%) had a ureteral stent put in place post-operatively [6].

It was our aim in this research to investigate which criteria independently influence the formation of ureteral lesions. Defining risk factors is also important in light of the fact that even ureteral lesions that do not perforate the ureter (PULS 1 and 2, Fig. 1) trigger later complications – especially strictures – that may cause the need for complex reconstructive surgery [12]. One of our study hypotheses was that preoperative ureteral

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p value/p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, cont. in years</td>
<td>1.01 (0.99–1.02)</td>
<td>0.551/0.558</td>
</tr>
<tr>
<td>Females (ref.: males)</td>
<td>1.42 (0.81–2.49)</td>
<td>0.217/0.247</td>
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<tr>
<td>Body mass index, cont., kg/m²</td>
<td>0.97 (0.93–1.01)</td>
<td>0.162/0.167</td>
</tr>
<tr>
<td>ASA-score 3+ (ref.: 1–2)</td>
<td>0.90 (0.45–1.79)</td>
<td>0.768/0.765</td>
</tr>
<tr>
<td>Hospital–volume of URS in 2015, cont</td>
<td>1.00 (0.99–1.01)</td>
<td>0.969/0.969</td>
</tr>
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<td>Urology speciality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assisting physician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 specialist years</td>
<td>1.05 (0.54–2.03)</td>
<td>0.893/0.898</td>
</tr>
<tr>
<td>&gt;5 specialist years</td>
<td>1.22 (0.62–2.39)</td>
<td>0.568/0.586</td>
</tr>
<tr>
<td>Pre-URS stenting (ref.: no stent)</td>
<td>1.49 (0.71–3.12)</td>
<td>0.290/0.294</td>
</tr>
<tr>
<td>Kidney stones (ref.: one ureteral stone)</td>
<td>0.81 (0.43–1.56)</td>
<td>0.538/0.528</td>
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<tr>
<td>Multiple calculi (ref.: singular)</td>
<td>0.78 (0.39–1.54)</td>
<td>0.474/0.517</td>
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<tr>
<td>Stone size, continuous in mm</td>
<td>1.06 (0.99–1.14)</td>
<td>0.090/0.081</td>
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<tr>
<td>Elective OP-indication (ref.: acute)</td>
<td>0.56 (0.24–1.28)</td>
<td>0.167/0.156</td>
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<tr>
<td>Flexible instrument (ref.: rigid only)</td>
<td>0.89 (0.45–1.74)</td>
<td>0.734/0.766</td>
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<td>Disintegration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Laser</td>
<td>3.62 (2.01–6.54)</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Ballistic</td>
<td>3.86 (1.23–12.12)</td>
<td>0.021/0.012</td>
</tr>
</tbody>
</table>

* Second p value reflects the result’s significance according to the Bootstrap analysis from 1,000 re-samples. Variables with significant influence are highlighted in italics.

PULS, post-ureteroscopic lesion scale; ASA, American Society of Anesthesiologists; URS, ureteroscopy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p value/p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-URS stenting (ref: no stent)</td>
<td>0.86 (0.35–2.12)</td>
<td>0.750/0.756</td>
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<td>Stone size, continuous in mm</td>
<td>0.96 (0.85–1.09)</td>
<td>0.519/0.416</td>
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<td>Disintegration</td>
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<tr>
<td>None</td>
<td>Reference</td>
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<tr>
<td>Laser</td>
<td>3.06 (1.06–8.79)</td>
<td>0.038/0.030</td>
</tr>
<tr>
<td>Ballistic</td>
<td>5.84 (1.42–23.95)</td>
<td>0.014/0.002</td>
</tr>
</tbody>
</table>

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PULS, post-ureteroscopic lesion scale; URS, ureteroscopy.
stents might significantly lower the probability of damaging the ureter during URS. Nearly 3 out of 4 of our study patients received a preoperative ureteral stent. According to the international literature, studies have shown that preoperative ureteral stenting correlates with greater patient safety (measured by the rate of complications) and therapeutic efficacy (determined by the stone-free rate) [13–17]. Preoperative ureteral stenting revealed no significant influence in relation to our study’s 2 endpoints (PULS 1+ and PULS 2+). We noted an independent increase in ureteral damage in PULS grades 1+ and 2+ only in conjunction with intracorporal lithotripsy. Compared to stone extraction using an ureteroscopic forceps or retrieval baskets without disintegration, the use of laser is associated with a 3.6-fold higher probability (p < 0.001) and ballistic lithotripsy with a 3.9-fold higher (p = 0.021) probability of presenting a PULS 1+ grade; similar ORs apply to PULS 2+: 3.1 (p = 0.038) and 5.8 (p = 0.014). There was no significant difference between the 2 disintegration procedures investigated in this study in terms of our 2 endpoints. According to the latest published international reports, both laser and ballistic lithotripsy are safe and effective means of disintegrating stones – the difference between them being marginal regarding patient safety and therapeutic efficacy [18–23]. Li et al. [23] compared the pneumatic and laser-assisted disintegration of medium and distal ureteral stones. Their analyses reveal somewhat greater efficacy and a higher stone-free rate in conjunction with the laser-assisted method, but the Holmium-YAG-Laser was also associated with a somewhat higher rate of postoperative ureteral strictures [23]. Our study patients’ long-term follow-up data will eventually reveal the impacts that minor ureteral lesions have (PULS 1–2), namely, the development of late complications. Our short-term follow-ups have so far failed to reveal a significant correlation between the PULS grades and complication rates (according to the Clavien-Dindo classification) [6].

Several study limitations should be considered before interpreting our BUSTER trial results. Although this was a prospective multicentric and homogeneous collection of data involving standardised criteria, our study protocol gave the participating centres a certain degree of flexibility (i.e., in choosing intraoperative equipment, the lithotripsy procedure, pre- and postoperative ureteral stenting, etc.). While such differences may have influenced our results, they also reveal the variety of approaches in different clinical settings in performing URS and thus extend our findings’ generalisability. Moreover, the technical specifics regarding the laser and ballistic lithotripsy groups were not precisely documented, although we know that the Holmium-YAG-Laser was usually employed in the laser group and that the second group’s lithotripsy was exclusively pneumatic. Another study limitation is the lack of long-term follow-up or reports of complications that might correlate with PULS grades. We are planning to follow-up these BUSTER study patients over the long term [7]. Our study’s low number of stone treatments needs to be considered; an a-priori power analysis (considering the low rate of events we anticipate) delivered a case load of 263 patients [7]. Our 307 trial patients were not recruited consecutively. Of the 587 patients who underwent URS therapy in this trial’s participating centres during the observation period, only 307 were willing to fill out the questionnaire 30 days after the procedure. This meant that 47.7% of the consecutive patients at the 14 participating centres had to be excluded.

Conclusions

The PULS scoring system is a standardised and reproducible tool to classify and document intraoperative ureteral lesions after URS. Although most such lesions are minor, intracorporal lithotripsy procedures independently cause urothelial damage. Preoperative ureteral stenting does not lower the probability of triggering intraoperative PULS 1+ and PULS 2+ lesions. Against the background of an increasing incidence, prevalence, and recurrence rate of urolithiasis as well as the increasing utilisation of URS, our data emphasise the need of multicentre prospective studies to evaluate the importance of ureteral lesions of any extent in the long-term course following ureterorenoscopic stone treatment.

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References


Ethics Statement
No humans or animals underwent any experiments in conjunction with this investigation.

Disclosure Statement
The authors of this paper have no conflict of interest to declare.

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Authors Contribution
Protocol and project development, design of the article: S.L., M.M., and M.S.; Data collection, data management: C.G. and J.P.; Data management, analysis of the data: M.M., A.M., and M.S.; Manuscript writing, manuscript editing: S.L. and P.-F.M. All authors reviewed the manuscript.