Evaluation of endourological tools to improve the diagnosis and therapy of ureteral tumors – from model development to clinical application

Abstract: Adequate diagnosis of upper urinary tract (UUT) tumors is essential for successful local treatment. Organ-sparing approaches are technically difficult and require consistent further development. Appropriate models for investigating new diagnostic and therapeutic methods are not yet available. This study demonstrates the incorporation of a fresh sample model into five different test levels (I-V) for improving the diagnosis and therapy of ureteral tumors. In these test levels, new diagnostic and ablation techniques are evaluated for feasibility, application safety, efficacy and accuracy. An assessment of their suitability for broad preclinical and clinical application also took economic aspects into account.

Keywords: preclinical model; intraureteral ultrasound; intraureteral laser therapy; fresh sample model; endourology

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1 Introduction

Adequate diagnosis of upper urinary tract (UUT) tumors is essential for successful local treatment and organ preservation. Due to the existing diagnostic uncertainty, many patients with ureteral (UR) tumors are still overtreated, which means they undergo nephroureterectomy. Nephrectomy involves dialysis at worst. Conventional imaging (magnetic resonance tomography, computed tomography, extracorporeal ultrasound) are still limited in terms of resolution and diagnostic adequacy [1]. However, diagnostic uncertainty is only part of the problem. Organ-sparing interventions in the upper urinary tract (UUT) are technically difficult and also require consistent further development. There is still a lack of appropriate models for evaluating new diagnostic and therapeutic procedures as well as practical training in their endourological application [2, 3]. This study demonstrates the incorporation of a fresh sample model, developed according to the identified demands, into the respective test levels: I – “Endourological model–UUT”, II – “Intraureteral ultrasound (IUUS)”, III – “Intraureteral laser therapy (IULT)”, IV – “First in men - safety/feasibility (IUUS/IULT)”, and V – “First in men - accuracy/efficacy (IUUS/IULT)”. An assessment of their suitability for broad preclinical and clinical application also took economic aspects into account.

2 Material and methods

2.1 Level I: endourological model–UUT

Aim: Development and production of a multifunctional endourological and practice-equivalent training model (Figure 1). Material: Transparent gel box for holding fresh samples (nephroureteral model “Deutsches Landeswesen”), with two hydrogel phases for in situ simulation. The standard endourological instruments (Carl Storz, Tuttingen, Germany; Uroskop Omnia, Siemens, Erlangen, Germany) and the validated questionnaire “Objective
Structured Assessment of Technical Skills (OSATS)” were used to evaluate 15 surgeons in 3 groups with different training levels [4]. Methods: Three training blocks (OSATS and intervention time) were evaluated in the model before and after training (specialist instructions, 60 minutes): 1. Contrast-enhanced imaging of the ureter (UR) and pelvicalyceal system (PCS), placement of a safety wire and rigid ureterorenoscopy (rURS). 2. Placement of a sluice in the renal pelvis via wire, complete inspection of the PCS with a flexible ureterorenoscope (fURS). 3. Disintegration of a kidney stone by laser and removal of 2 concrements (Figure 3).

2.2 Level II: intrarenal ultrasound (IUUS)

Aim: Evaluation of intravascular ultrasound (IVUS) in the fresh renal sample model for ureteral diagnosis (IUUS). Material: Volcano CORE™ Mobile (Volcano Corp., USA); ultrasound catheter (Eagle Eye® Platinum ST, Visions® PV .018 and Visions® PV .035 (Volcano Corp., USA); Volcano Trak Back II, (Volcano Corp., USA). Endourological model- UUT, test specimens. Methods: IUUS with various IVUS catheters, assessment of subjective visual impression, distinguishability of individual UR wall layers and UR surroundings (test specimens) by 3 trained endurologists in a consensus procedure. Comparison with histological wall structure (Figure 2).
2.3 Level III: intraureteral laser therapy (IULT)

Aim: Evaluation of diode laser (IULT) in the endourological model-UUT for organ-sparing treatment of ureteral tumors, temperature behavior. Material: Compact Laser DIOLAS Photon (Limmer Laser, 980 nm, Berlin, Germany) TempSens72® (Opsens®, Quebec, Canada), Endourological model-UUT, test specimen. Methods: Defined UR lasering of the urothelial and deeper wall layers with various energy levels (3-30W), measurement of local energy input (temperature measurements), histological comparison.

2.4 Level IV: first in men- safety/feasibility (IUUS/IULT)

Aim: Use of an IVUS system to visualize UR wall layers (IUUS) in a clinical “all-in-one setting” with application of the Limmer Laser for IULT. Examination of feasibility and patient safety. Material: Volcano CORE™ Mobile (Volcano Corp., USA); ultrasound catheter (Eagle Eye® Platinum ST, Volcano Corp., USA), Compact Laser DIOLAS Photon, Harpoon Fiber 400 µm (Limmer Laser, Berlin, Germany), endourological workplace (Uroskop Omnia, Siemens Healthcare, Erlangen, Germany), flexible ureterorenoscope (Flex x², Carl Storz, Tuttingen, Germany), Access Sheath (10/12 Charr., Coloplast, Hamburg, Germany), standard urological instruments. Methods: To exclude infiltration, 5 patients with confirmed urothelial carcinoma in the UUT underwent IUUS as well as the standard diagnostic procedure in order to provide legitimization for an “individual curative attempt”. After confirmation, conservative IULT was performed using the Limmer Laser and Harpoon Fiber.
2.5 Level V: first in men-accuracy/efficacy (IUUS/IULT)

Aim: Examination of diagnostic (IUUS) and therapeutic (IULT) accuracy and efficacy in the context of a “second look”. Material: Analogous to section 2.4. Methods: Five patients diagnosed and treated in the context of an “individual curative attempt” (see section 2.4) again underwent IUUS as well as the standard diagnostic procedure 8-12 weeks later. After excluding infiltration, persistent residual findings were again treated with the Limmer Laser. The degree of efficacy (tumor reduction or removal) was assessed and documented by two experienced endourologists.

3 Results and discussion

3.1 Level I: endourological model –UUT

Result: In its production and application, the “endourological model-UUT” proved to be an inexpensive, simple and robust experimental setup that easily enabled stepwise evaluation of test subjects. Functionality for at least 2 days could be ensured when using fresh samples. It was assessed by all test subjects and evaluators as suitable for the subsequently planned examinations (Level II and III). The OSATS evaluation before and after training in the model revealed marked improvement in the required skills. Discussion: Available training models for the UUT are expensive and impractical [2, 3]. The “endourological model – UUT” enabled practical training in a typical endourological setting. Marked shortening of the learning curve was detectable (Figure 4). Technical improvements without great effort or expense are planned. A limiting factor was the absence of blood flow and respiratory movement in the model.

3.2 Level II: intraureteral ultrasound (IUUS)

Result: With the “endourological model-UUT” modified by test specimens, IUUS examinations could be performed for all US catheters in a robust and standardized manner (automatic US catheter pullback: 1mm/s, 15fps). The investigation focused on visualization of the urothelium and the adjacent muscle layer. Subjectively, the UR wall layers could be distinguished most precisely with the US catheter “Eagle Eye® Platinum ST”. Its US images were
therefore used for histological comparison. The test specimens could be visualized in the UR surroundings in relation to device settings/catheter (Figure 5). Discussion: Our results suggest that therapeutically relevant tumor infiltrations of these layers can probably be visualized in the human UR; an investigation in a clinical setting should therefore be performed in Levels IV and V. Various study groups have already examined other intraluminal US catheters in a preclinical and clinical setting [7, 8]. Due to the small number of cases, the assessment of suitability for clinical application remained open.

3.3 Level III: intraureteral laser therapy (IULT)

Result: In the “endourological model-UUT”, IULT could be performed easily for defined energy levels (3, 10, 15, 20 watts). Laser ablation restricted to the urothelial layer succeeded subjectively with 3W. Ablations of solid tumors (5-10 mm) required 10-15W. At 20W, dosed energy output for targeted ablation was complicated (adhesions). Temperature elevations measured at the outer surface of the UR during local laser applications remained below the denaturation level (15 W, 980nm, continuous mode). Discussion: The application of laser energy with an angled Harpoon Laser tip enables subtle tissue ablation. Comparative studies of other laser types describe acceptable side effects (SE) [11]. Subjectively improved SE in our examinations therefore enabled application in a clinical setting in Levels IV/V.

3.4 Level IV: first in men - safety/feasibility (IUUS/IULT)

Result: As expected, IVUS catheter placement for IUUS succeeded easily in an endourological setting when applied in humans (5 patients) owing to the catheter dimensions and application similarity (intravascular-intraureteral). Visualization of the wall layers succeeded subjectively better than in the “endourological model-UUT”; infiltration of the muscle layer could be excluded in both the IUUS and the standard biopsy (Bx)/urine cytology. Local tumor lasering was therefore carried out using the Limmer Laser (Harpoon Fiber, R 400 µm). Papillary tumors up to 5mm could be ablated very precisely to the muscle level of the UR (3 W, 980 nm, continuous mode). There was no intraoperative damage to surroundings. Solid findings (5-10 mm) required higher energy levels (10-15W, 980nm, continuous mode, pulsed mode) for complete ablation. The angled laser tip (30°) enables very precise layerwise ablation of tumor tissue in both continuous and pulsed mode. Both IUUS and IULT proved to be simple and safe methods for human application. The actual efficacy (tumor ablation) and accuracy (damage to surroundings) of the two methods should be established in the recommended standard endourological follow-ups (Level V). Discussion: Placement of the IVUS catheter in an IUUS setting does not differ from typical endourological procedures, and the better spatial resolution enabled a more detailed diagnosis than that achieved with currently recommended imaging. Various study groups have already tested other intraluminal US catheters (30MHz,
5F, B-mode; 12.5/20MHz, 6.2F) for detailed diagnosis of UR tumors [7, 8]. IULT management and ablation behavior made it possible to ablate even larger tumors with simultaneous hemostasis and no collateral damage. The applied 400 µm laser fiber permitted controlled flexion of the fURS for lasering lower calices. The angled laser tip offers marked advantages over other commercially available systems [5, 6].

3.5 Level V: first in men- accuracy/efficacy (IUUS/IULT)

Result: The endourological follow-ups 8-12 weeks after the primary intervention (IUUS, IULT) showed good tumor control in all patients. Small papillary findings had disappeared completely in the optically regenerated urothelial layer. After lasering several large (5-10 mm) solid findings, two small residual solid tumors were seen in 1 case. Re-examination for possible infiltration into deeper wall layers after standard Bx/urine cytology and IUUS remained
The residual findings were again submitted to IULT with the Limmer Laser (Harpoon Fiber, $\lambda$ 400 μm, 3–10W, 980nm, continuous mode, pulsed mode). This patient was also tumor-free after another 8 weeks. Imaging of the wall layers also succeeded subjectively better after primary therapy (IULT) than in the “endourological model-UUT”. Both IUUS and IULT proved to be accurate and effective in tumor therapy. The “third look” disclosed no evidence of damage to surroundings. Discussion: Investigations on the long-term follow-up of laser-treated UR tumors are rare [9, 10]. Guidelines for IUUS diagnosis are lacking, and they are vague for IULT due to a lack of data [1]. With strict indications, good tumor control with organ preservation could be achieved in our cohorts (Figure 6). Side effects did not occur and are also assessed as minimal in the literature [11]. Limiting factors were the small number of patients and the short follow-up.

4 Conclusion

Our endourological model-UUT can be safely and effectively used as a training tool to shorten learning curves. Endourological techniques and conservative tumor treatment in the upper urinary tract is an evolving field and can be successfully used as first-line treatment for UUT tumors in selected patients. Recent technical advancements should now be consistently investigated and standardized with regard to diagnosis and therapy.

Author’s Statement

Conflict of interest: Authors state no conflict of interest. Material and Methods: Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.

References