

THULIUM LASER ENDOSCOPIC EN-BLOC ENUCLEATION OF NON MUSCLE-INVASIVE BLADDER CANCER (ThuLEBT)

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ABSTRACT

Objectives

To evaluate if thulium laser enucleation of bladder tumor (ThuLEBT) offers any advantage over monopolar resection of non muscle-invasive bladder cancer (NMIBC) without increasing complications.

Patients and Methods

From February 2012 to September 2013, 58 patients (41 male and 17 female) newly diagnosed with single papillary bladder tumor more than 1 cm in diameter were selected for this prospective study on ThuLEBT. A similar historical cohort of 61 patient who underwent traditional monopolar resection (TURB-T) of NMIBC (Group B) was used to compare the two procedures .

Results

Mean tumor diameter in ThuLEBT group was 2.5 cm (range, 0.5-4.5). Mean operative time was 25 minutes (range, 12-30). Re-resection and cold-cup biopsy of the tumor base (in 90 days) was negative for BC persistence or recurrence in all patients with NMIBC treated with ThuLEBT. In group B seven patients were found with a disease persistence. In 8 cases of TURB-T patients no detrusor muscle was identified while it was always easily identified in ThuLEBT group. No patient in group A experienced obturator nerve reflection intraoperatively and no bladder perforation were evidenced in dome located neoplasm; when involved, ureteral meatus was sharply excised without

subsequent post-operative evidence of distortion. No significant intraoperative or postoperative bleeding occurred in all but one patient in the two groups.

Conclusion

ThuLEBT may represent a potential alternative to TURB-T which nowadays is considered the standard for diagnosis and treatment of NMBIC. In our study ThuLEBT allowed accurate reporting of neoplastic depth invasion suggesting the possibility to avoid a second look resection at 90 days. All the different intravesical site of the BC may be enucleated with the thulium laser which offers advantages over the monopolar energy especially when the tumor is located in the lateral bladder wall, at bladder dome or in perimeatal zone.

Introduction

Transurethral resection of bladder tumor (TURB-T) is considered nowadays the gold standard for management of bladder cancer (BC), but there is evidence of a high rate of tumor recurrence after primary resection, and of variation between institutions [1]. Surgical accuracy is paramount to the safety and efficacy of TURBT, but technical and procedural considerations may also have an impact on outcomes. A second resection may improve staging and tumor removal [2], particularly where the primary procedure was affected by multiple tumors, large tumor bulk, bleeding during resection, bladder perforation, patient habitus, or anaesthetic risk, or if the patient has high-risk bladder tumor, T1 tumor, multiple high-grade Ta tumors, or carcinoma in situ. The standard TURB technique involves piecemeal resection of the tumor, which runs counter to established oncological principles of removing tumor intact as the piecemeal approach liberates tumor cells into the bladder. In view of this issue and of the high rate of recurrence, several studies have examined the feasibility of a modified TURB to provide en bloc resection of the specimen, based on the established oncological principle of dissecting through normal tissue. The researched final results is to allow en-bloc sculpting and resection of the tumor. We describe a technique of bladder tumor en bloc enucleation with a new double wavelength thulium laser (ThuLEBT). During cutting activity of the Multipulse Tm+1470 Thulium laser, diode and thulium laser work together mixing their effects at the same time. This offers the possibility of a planned hemostatic enucleation through the bladder musculature and of a very efficient coagulation of the bed of resection. Results were compared to an historical control group treated by

conventional TURBT. Aim of the paper is to evaluate if this planned deep enucleation offers a more precise pathological tumor stage without increasing the risk of bladder perforation, pros and cons of the laser procedure in respect to tumor location and size and its impact on the risk of tumor persistence at 90 days re-resection with cold cup biopsy of the previous tumoral area.

Patients and Methods

From February 2012 to September 2013, 58 patients (Group A : 41 male and 17 female) newly diagnosed with single papillary bladder tumor more than 1 cm in diameter were selected for this prospective study on ThuLEBT. Mean patient age was 71 years (range, 35-86). Exclusion criteria were multiple or recurrent NMIBC, suspect of locally advanced BC (cT2 or higher) at CT examination, and/or distant metastases. A similar historical cohort of 61 patients who underwent monopolar resection of NMIBC (Group B) by the same surgeon from April 2011 to February 2012 was used to compare the two procedures (Table 1).

Preoperative evaluation included clinical history, physical examination, ultrasound examination of the bladder, flexible cystoscopy and urine cytology. Abdominal computed tomographic scan was performed only in selected case. All patients signed an informed consent.

TURB-T was made according to the EAU guidelines. ThuLEBT was performed with the patient in the lithotomy position under spinal anesthesia, with normal saline solution as continuous irrigation. A 600-nm laser fiber introduced in the working element of a 26 F continuous-flow resectoscope (Olympus, Hamburg,

Germany) was used. The fiber was connected to the Multipulse Tm+1470 Thulium laser (Multipulse Tm+1470, Asclepion, Jena, Germany), equipped with a 1940 nm thulium laser, and an associated 1470 nm diode laser (Raman module). Laser was used in the continuous-wave setting at 30 W with a Thulium frequency of 50 Hz during the enucleation and switched to the 1470 nm diode laser during coagulation by a foot pedal. Procedural steps (Figures 1 and 2) included firstly a circumferential tattooing incision around the tumor with a safety margin of normally appearing mucosa of approximately 5 mm. After that, resection proceeded toward the deeper layers of the bladder wall (down to the adventitial layer), combining the laser incision with the blunt dissection of the resectoscope tip. The resection through the bladder wall was more superficial along the peripheral part of the tumor and proceeded deeply toward the adventitial plane moving from the periphery to the center of the tumor base to enucleate the tumour. The tumor, along with its base, was retrieved in one piece through the resectoscope sheath, or sometimes removing the entire resectoscope from the urethra, using a thick loop and engaging the fragment between the beak of the instrument and the thick loop. When the tumor size was >3 cm, it was necessary to incise longitudinally and/or across the lesion and the bladder wall at the base into 2 or more parts. This operation was performed before completing the resection, with the neoplasm still in situ, to reduce the risk of tumor cell scattering. After resection, the tumor base was uniformly coagulated using the 1470 nm diode laser in the pulsed-wave setting at 20 W. A 20 Ch Foley catheter was inserted after the procedure with irrigation for 12 hours. The enucleated specimen was sent for histopathologic

examination. The 2009 TNM classification and the 2004 World Health Organization grading system were used for histopathologic examination.

According to our research protocol, a “second-look resection” preceded by a cold cup biopsy of the tumoral area, were performed within 90 days (see “Results”) in Group A NMIBC patients and results were compared to the similarly treated historical Group B (conventional TURB-T). Statistical analysis was performed using the chi-square test. The p value considered to be statistically significant was <0.05. Clavien Dindo analysis of complications was adopted.

Results

A total of 72 neoplasms were removed with THULEBT from 58 patients in Group A. Mean tumor diameter of the removed neoplasm in Group A was 2.5 cm (range, 0.5-4.5). The neoplasms up to 4.5 cm had a narrow base of implant. In Figure 3 is shown the depth of thermal damage induced by the laser energy on the bladder neoplasm base of implant.

The neoplasms were located on the trigone (16 cases, 7 of them close to the ureteral meatus), left lateral wall (15 cases), right lateral wall (11 cases), posterior wall (14 cases), and bladder dome (12 cases). Mean operative time was 25 minutes (range 12-30). No patient experienced obturator nerve reflection intraoperatively. No significant intraoperative or postoperative complications occurred (see table 2).

According to the Clavien Dindo classification for surgical complications, no complications occurred in Group A (Grade I), while 2 patients in Group B

(TURB-T) required blood transfusions (Grade II) and one patients in Group B required an endoscopic haemostasis (Grade III).

In patients with papillary lesion covering the ureteral meatus (UM), after placing a nitinol guide wire into the meatus using the same laser fiber operative support , BC was removed in two cases enclosing the meatus itself while in the remaining cases UM was saved with a great precision. In no cases a ureteral stenting was necessary .

Mean catheterization time was 28 hours (range, 24-32)in group A and 38 (range 29-48) in group B. Mean hospital stay was 47.5 hours (range, 36-96) and 58,5 hours (range 40-98) respectively in Group A and B. Pathologic results in Group A showed urothelial carcinoma with stage Ta low grade in 30 patients (56.4%), T1 high grade in 23 patients (32.7%), and T2 high grade in 5 patients(10.9%). Apart from neoplasm covering the ureteral meatus, histopathologic evaluation demonstrated that the bladder detrusor was provided in all cases in Group A while it was absent or not valuable (due to thermic artifacts) respectively in 5 and 3 Group B patients. Re-resection and cold-cup biopsy of the tumor base (in 90 days) was negative for BC persistence or recurrence in all patients with NMIBC treated with ThuLEBT while positive tumor ground biopsies were found in 7 of Group B patients . In three of them there was an upstaging from Ta to T1 and in one case from T1 to T2. After a mean follow-up of 20 months (range, 13-25), we found recurrences in 12 of 58 patients (20.6%) of Group A, without progression in tumor grade. All recurrences were not at the primary resection site. The 18-month recurrence-free survival was 90% among patients with

primary Ta BC and 76% in the group of patients with primary T1 BC. ($p=ns$). The risk of recurrence was similar to historical Group B TURB-T control.

Four out of twelve patients with bladder neoplasms > 3 cm who underwent splitting of their BC during resection had T2 high grade BC and, consequently, underwent cystectomy. We had 2 recurrences at follow-up among the remaining eight patients who needed “splitting” during primary resection and 5 recurrences among the 46 patients who did not need tumor “splitting”. The difference was not statistically significant ($p=0.6$). In Table 1 and 2 are reported the clinical features of historical control group (Group B) patients.

Discussion

Herr in 2005, after a previous report on the value of a second transurethral resection in evaluating bladder cancer patients described residual rates of 15–53% at second TURB, and upstaging rates of 4–29%, with muscle invasion [3]. In many cases that are upstaged after second resection, it is apparent that muscle was not present in the original resection. The quality and result of the initial transurethral resection via a wire loop (TURB-T) strongly determines the patient’s prognosis. An unshakeable principle of the surgical treatment of cancer is to dissect through normal tissue and to remove the tumor with a negative margin. Moreover it has been demonstrated that TURB-T does affect the volume of viable tumor cell released during tumor resection in animals: conventional TURB-T released 620% more tumor cells than neodymium laser irradiation of the tumor [4]. Several studies have examined the feasibility of various en bloc resection techniques. Ukai et al. [5-6] described the technique

almost 15 years ago, using a J-shaped needle electrode, while Saito et al. [7] was the first to present results on a holmium:YAG laser *en bloc* resection of the tumour. Wolters et al. [8] adopted *en bloc* tumour enucleation as described by Ukai et al. using a thulium laser to perform the mucosal incision and was able to demonstrate detrusor muscle in all cases, proposing the potential for exact staging at the time of initial TURB-T.

Positive histopathological results were reported in conjunction with laser *en bloc* resection of bladder cancer. Lowering of thermal damage improved pathohistological staging [9]. Particularly the application of Tm:YAG showed precise cutting, thus avoiding tumor damage and this may contribute to explain the higher T1 NMBIC discovered in ThuLEBT group if compared to TURB-T historical cohort.

During cutting activity of the Multipulse Tm+1470 Thulium laser we used, diode and thulium lasers work together mixing their effects at the same time (this is a peculiarity of this laser). The clear and precise cutting effect of the thulium laser are related to its 1940 nm wavelength with approximately 0.2 mm depth of thermal damage. 1470 nm diode laser is readily absorbed by water allowing for low-char hemostatic tissue removal with a thermal damage of about 0.4 mm. The mixed effects of the two lasers simultaneously seal off the blood vessels to minimize bleeding during cutting. Diode laser energy alone is activated during pure coagulation.

A further potential benefit of using the *en-bloc* laser enucleation of the tumor over conventional wire-loop resection is that *en-bloc* enucleation improve specimen orientation, making histological reporting more straightforward. The

technique appears to allow accurate reporting of depth invasion [10], and we also confirm that re-resection and cold-cup biopsies of the tumor base in ThuLEBT group did not alter the diagnosis or stage in any patients confirming previous data. This means that as ThuLEBT allows accurate reporting of depth invasion the need to restage bladder tumor at 30 to 90 days may be reevaluated.

Besides tumor size, one of the major drawbacks for laser en bloc resection has been the intravesical tumor localization. Several research groups excluded tumor resection at the bladder dome wall which implicated the risk of peritoneal damage [11-12]. We do not agree with them as in our experience ThuLEBT was more easily and precisely conducted than monopolar TURB-T. The absence of bleeding let us to improve visualization of the different planes during anterior bladder wall enucleation and as thermal injury due to thulium laser wavelength is only 0.2 to 0.4 mm in depth, the risk of transparietal thermal damage of the neighboring tissue (i.e. ileal loops) is negligible. Of great interest was also the possibility to sculpture the ureteral meatus avoiding the charring induced by monopolar energy in case of meatal bladder cancer. Even if 7 cases are few, no distortion or stenosis of the meatus was evidenced at 90 days re-evaluation of the tumoral area. Overall 6 meatal BC treated by TURB-T resulted in one meatal stenosis. The absence of obturator kicks in patients with lateral wall neoplasm is another advantage of the laser energy evidenced by some authors [12-13-14]. Comparing conventional TURB-T to Thulium laser en bloc resection of bladder tumors a significant reduction of obturator nerve reflex related

bladder perforations was evident. Overall, 8 obturator nerve stimulations resulted in 3 bladder perforations using conventional TURBT in our experience. Even if another drawback of en bloc resection is the fear of the complications due to the deepness of the treatment, to date, complications in conjunction with en bloc resections in literature have been described in only four of a total of 459 patients. This makes an overall complication rate of 0.7%, of which all complications had not been life-threatening. Intra-, peri- or postoperative bleeding were rare in laser en bloc resections. This confirms the known powerful hemostatic effect of Tm:YAG laser which led to a reduction in postoperative bladder irrigation time in comparison with conventional TURB.

Tumour size was also not a problem in our experience. While Nagele et al. extracted tumors up to 2 cm [15], Fritsche and colleagues performed en bloc resection up to 7.5 cm showing that en bloc resection of tumors > 4.5 cm is possible [16]. In our experience, although resecting tumors >3 cm, R0 resection was achieved in all our cases.

Also, en bloc resection using monopolar current showed good results [5-7]. In three of the initial four reports, all specimens were R0 and included detrusor muscle. However In Ukai's second case series, 93% of the 90 patients revealed negative control biopsies from the tumor ground [6] and of the remaining seven patients with positive tumor ground biopsies, five patients had a pT2 tumor and two patients had a minimum pT1 tumor in the final histopathology. Also, using this technique, the pathologic interpretation was limited in one of 11 tumors due to crush injury of a very small lesion [17] and in five of 11 tumors interpretation of detrusor muscle was not possible because of electrocautery injury. Finally, in

spite of a decreased recurrence rate reported within ThuLEBT group in comparison to conventional TURB-T the significance level was not reached.

Conclusions

En-bloc laser enucleation of bladder tumors is an interesting potential alternative to TURB-T which nowadays is still considered the gold standard for diagnosis and treatment of NMBIC. The feasibility of laser en-bloc enucleation without the risk of perforation has been demonstrated. All the different intravesical site of the BC may be enucleated with the thulium laser which offers some clear advantage over the monopolar energy especially when the tumor is positioned in the lateral bladder wall or in the bladder dome or in perimeatal zone. One advantage of the Multipulse Tm+1470 Thulium laser is that it allows for minimal transmural coagulative necrosis (about 0.2 mm) reducing the rate of perforation and extravasation and leaving a sharp boundary between the necrotic tissue and the surrounding tissue. A further potential benefit of ThuLEBT over conventional wire-loop resection is that it allows for accurate reporting of depth invasion opening the way to re-evaluate the need for restaging bladder tumor at 90 days. Even if recurrence rate was lower in ThuLEBT group the assumed oncologic benefits cannot be concluded from the available data in terms of recurrences as they are extremely heterogeneous with an obvious selection bias.

Acknowledgements

Dr. Roberto Migliari drew the anatomical pictures describing the ThuLEBT procedure.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations used in the text:

TURB-T - TransUrethral Resection of Bladder Tumor

ThuLEBT - Thulium Laser Enucleation of Bladder Tumor

NMIBC - Non Muscle-Invasive Bladder Cancer

BC - Bladder Cancer

UM - Ureteral Meatus

Tm:YAG – Thulium:Yttrium Aluminium Garnet

Ho:YAG – Holmium:Yttrium Aluminium Garnet

EAU – European Association of Urology

	THULEBT (GROUP A)	TURBT (GROUP B)
Patients (n°)	58 (41 M, 17 F)	61 (45 M, 16 F)
Mean age (yr)	71	72.5
Mean diameter of the neoplasm (cm)	2.5	2.3
Tumor location		
<i>Trigone</i>	16	18
<i>Left Lateral Wall</i>	15	12
<i>Right Lateral Wall</i>	11	14
<i>Posterior Wall</i>	18	20
<i>Dome</i>	12	11
Histopathology		
<i>Ta Low Grade</i>	30	38
<i>T1 High Grade</i>	37	33
<i>T2</i>	5	4
Bladder Detrusor		
<i>Provided</i>	58	53
<i>Not Valuable</i>	0	3
<i>Absent</i>	0	5

Table 1. Clinical features of Group A and Group B.

Journal of Endourology
Thulium laser endoscopic en-bloc enucleation of non muscle-invasive bladder tumor (ThuLEBT). (doi: 10.1089/end.2015.0336)
This article has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

	THULEBT (GROUP A)	TURBT (GROUP B)
Mean operative time (min)	25	20
Mean catheterization time (hr)	28	38
Obturator nerve reflection	0	8
Complications (Clavien Dindo)		
<i>Grade I</i>	58	55
<i>Grade II</i>	0	5
<i>Grade III</i>	0	1
<i>Grade IV</i>	0	0
<i>Grade V</i>	0	0

Positive 2nd look (after 90 days)	0	7
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Table 2. Comparison between ThuLEBT and TURB-T.

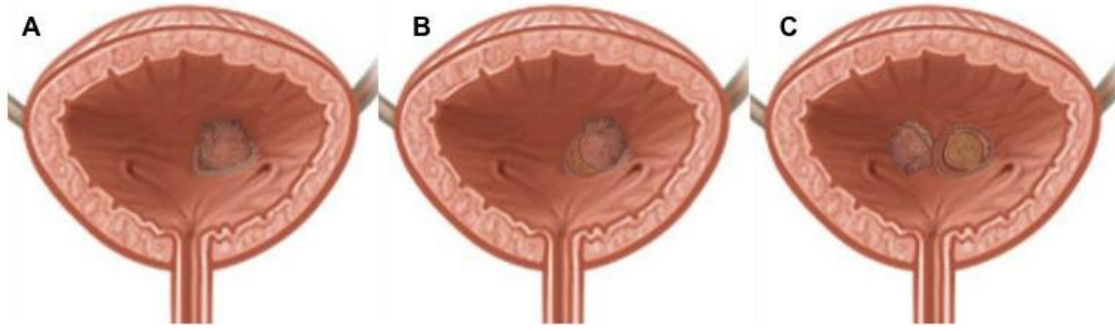


Figure 1. Main steps of ThuLEBT (illustrations courtesy of Dr. Migliari): tattooing (1A), en-bloc enucleation (1B) and end of the procedure (1C).

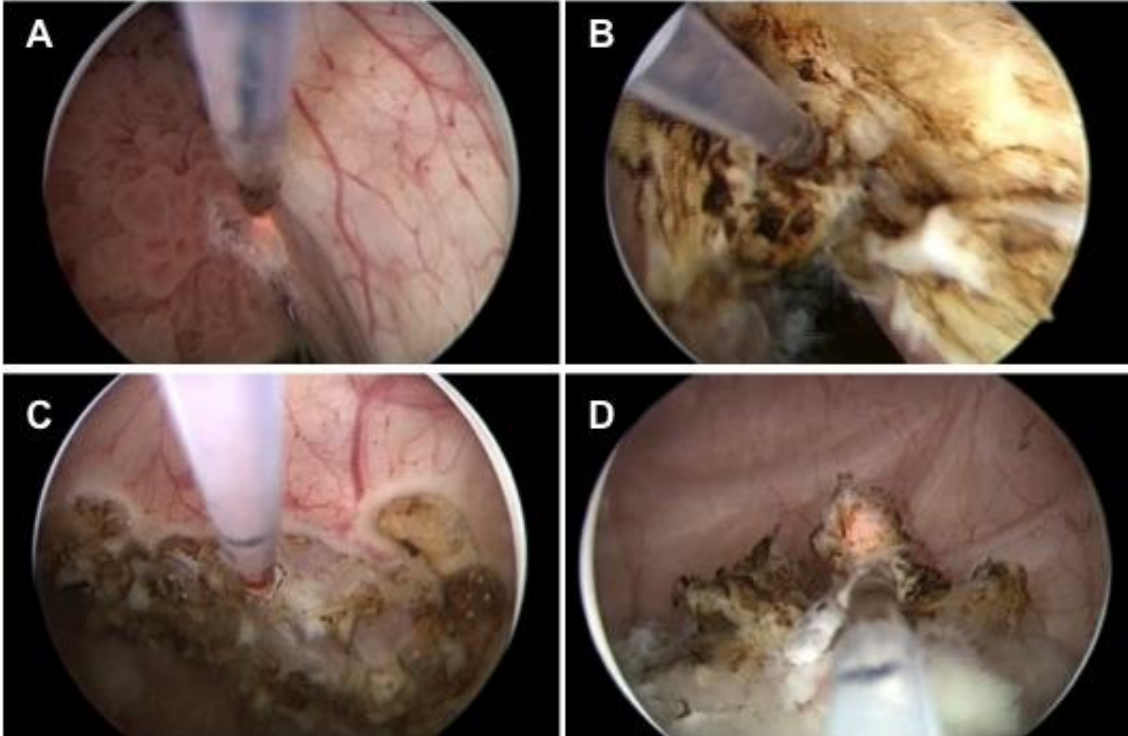
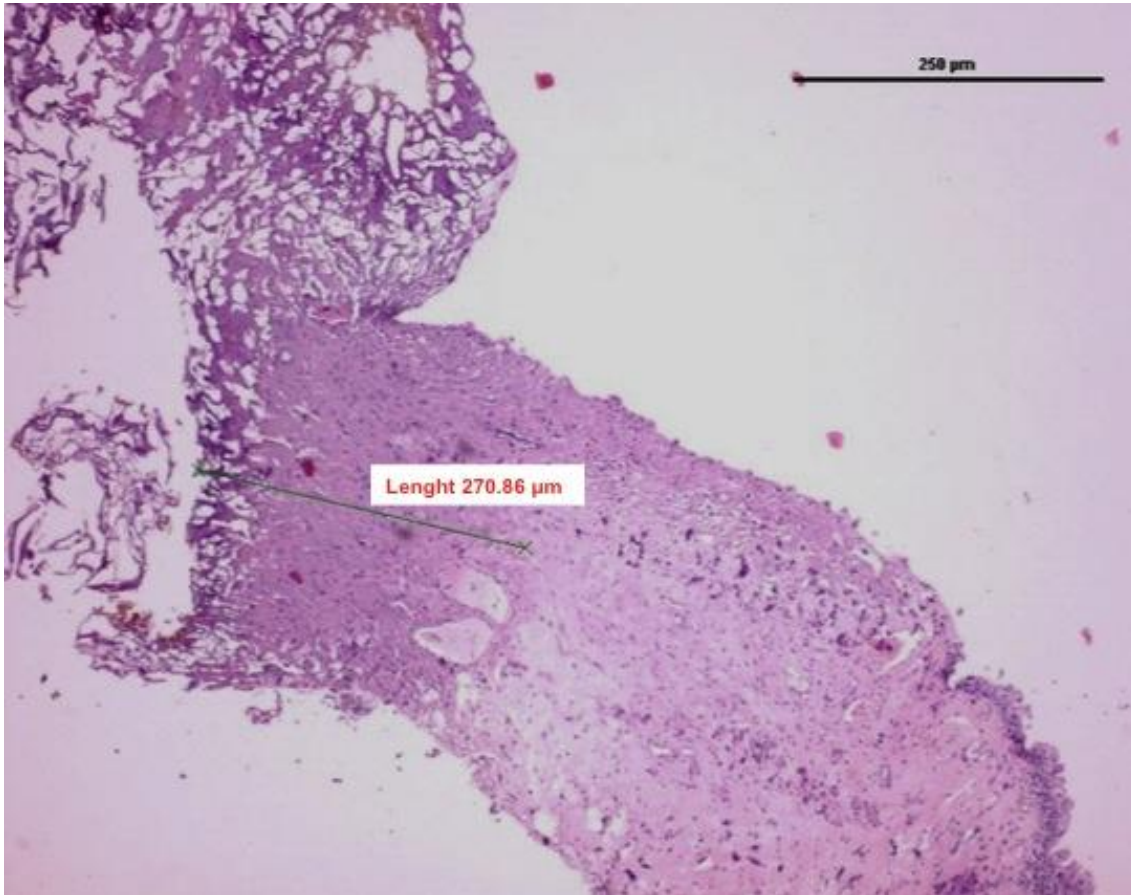


Figure 2. Thulium Laser Enucleation of a bladder dome tumor (intraoperative view): “tattooing” (2A), progressive en-bloc enucleation (2B), haemostasis (2C) and overview at the end of the procedure (2D).



Histological aspect of the laser induced thermal damage in a bladder neoplasm.