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NBI-assisted digital flexible ureteroscopy in transitional renal cell carcinoma – an evidence-based assessment "through the looking glass" of the pathological analysis

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Abstract

Introduction: Digital flexible ureteroscopy (FURS) increasingly became a routine diagnostic procedure in upper urinary tract transitional cell carcinoma (UUT-TCC). Identifying elements that may suggest the malignant nature of a lesion and obtaining biopsy specimens sufficient for a reliable pathological analysis remain difficult challenges. Narrow-band imaging (NBI) technology appears to provide a more accurate observation of the upper tract urothelium. *Patients, Materials and Methods*: During this prospective analysis, white light (WL) and NBI-assisted digital FURS were performed in 87 consecutive patients admitted for primary suspicion of UUT-TCC. The endoscopic technique comprised digital WL FURS, followed by the NBI assessment of the renal collecting system' mucosa. All suspicious areas of the pyelocaliceal urothelium were biopsied using the grasping forceps, separately for WL and NBI findings. *Results*: A total of 113 UUT-TCC tumors (104 pTa and nine carcinoma *in situ* – CIS) were confirmed by pathology in 62 patients. The patients' detection rate was significantly improved in NBI mode when compared to standard FURS (98.4% *versus* 91.9%, respectively), due to cases either exclusively diagnosed with UUT-TCC (8.1%) or presenting additional urothelial tumors (12.9%). Overall, 13 pTa and two CIS lesions were solely observed in NBI, which was on the other hand characterized by a significantly increased proportion of unnecessary biopsies (NBI *versus* WL rate of false-positive results – 17.5% *versus* 10.1%, respectively). *Conclusions*: As additional tool for the standard WL evaluation of the pyelocaliceal system' urothelium, NBI-guided biopsies were emphasized as providing a significant diagnostic improvement during digital FURS.

Keywords: digital flexible ureteroscopy, narrow-band imaging, transitional cell carcinoma, urothelial cancer.

Introduction

Transitional cell carcinomas represent up to 90% of all upper urinary tract tumors (UUT-TCC) [1] and constitute a rather redoubtable malignancy, especially due to the considerably thinner visceral wall of the upper tract when compared to the bladder, thus facilitating UUT-TCC progression somewhat earlier along the cancer specific natural history [2]. Like other types of carcinomas, various risk factors are involved in its appearance, like environment factors, heredity, hormonal changes and many others [3, 4]. It's a malignancy with a low prevalence but it is frequently multifocal being usually diagnosed in an advanced stage with various complications related to an impaired renal function or may furthermore complicate the evolution of patients with chronic renal failure [5–7] and it often makes the perioperative management of these patients very difficult [8–10].

During the recent years, digital flexible ureteroscopy (FURS) increasingly became a routine diagnostic procedure in UUT-TCC management, conventionally performed in white light (WL) [11]. Unfortunately, limitations are substantial when attempting to find small papillary tumors or even more so carcinoma *in situ* (CIS) lesions [12]. The latter category is widely recognized as difficult to identify, since it may just involve small flat areas of the urothelium solely differentiated by a redness aspect related to the increased vasculature in the submucosa [13].

Overall, identifying elements that may suggest the malignant nature of a lesion and obtaining biopsy specimens sufficient for a reliable pathological analysis and for eliminating others potential differential diagnoses remain difficult challenges [14–16]. So, narrow-band imaging (NBI) was introduced as a promising technological advancement, susceptible of providing a more accurate observation of the upper tract urothelium, while giving targeted biopsies a better chance to pathological confirmation [17].

The primary endpoint of the trial was to determine differences in UUT-TCC lesions' detection rates specific for WL and, respectively, NBI ureteroscopy, while assessing the eventual diagnostic progresses introduced by consistently

applying this adjunct endoscopic modality. Secondary endpoints referred to variations in the proportion of found urothelial cancer cases and specificity of the targeted biopsies, as shown by the frequency of false-positive results.

Patients, Materials and Methods

Based on the above premises, a prospective analysis was performed involving a total of 87 consecutive patients admitted for primary suspicion of UUT-TCC. The inclusion criteria consisted of pyelocaliceal system filling defects according to computed tomography (CT) results, unilateral hematuria during cystoscopy and abnormal urinary cytology. On the other hand, patients with CT aspects suggestive for invasive UUT lesions and cases of ureteral tumors were excluded from the trial.

Patients' inclusion in the study and the use of this additional diagnostic modality intended to eventually improve the WL evaluation were based on and following completion of an informed consent. The investigation protocol included abdominal ultrasound, cytology, contrast CT scan and cystoscopy. The endoscopic technique comprised digital WL FURS followed by the NBI assessment of the renal collecting system mucosa (Figure 1). Tumor visual characteristics according to the WL and NBI endoscopy were compared by repeated switching between the two vision modes while focusing on each suspected urothelial lesion.

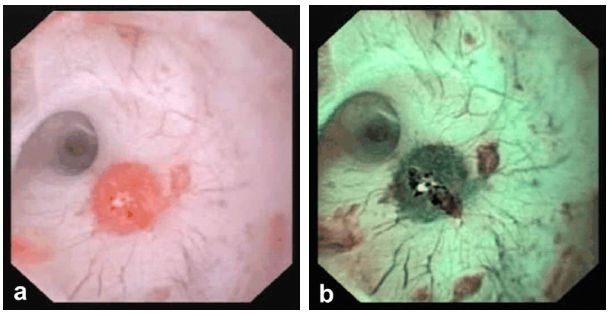

Figure 1 – ***pTa pyelic tumor identified both in WL (a) and NBI mode (b). WL: White light; NBI: Narrow-band imaging.***

Separate pyelocaliceal tumor maps of all identified lesions were specifically outlined for WL and NBI-assisted digital FURS. Subsequently, all suspicious areas of the urothelium were biopsied using the grasping forceps (Figure 2) separately for WL and NBI findings. More precisely, the biopsy specimens were registered in three categories: found in both WL and NBI, only seen in NBI and eventually observed solely in WL. The lesions were excised according to the same pathological map. The quantities of biological material were similar regardless of the utilized vision mode, as the biopsy taking method was the same (grasping forceps).

All the biopsy specimens were analyzed by two different pathologists with extensive experience in the field of UUT-TCC patients. In case of contradictory diagnostics, a third pathologist was called to re-evaluate the specimens. In order to address the issue of inter-observatory variability, debatable cases were viewed during the weekly Committee of the Department of Pathology.

Regarding the actual cancer-specific treatment, all the lesions were afterwards treated conservatively by holmium laser vaporization with a 275-µm laser fiber (Figure 3). As last stage of the digital FURS procedure, a final WL and NBI control was applied to all targeted areas of the mucosa searching for any remaining residual tumors/margins. Although rarely necessary, the laser coagulation of eventually existing bleeding sources was carefully applied. As a safety precaution, a JJ stent was mounted in each case at the end of the procedure.

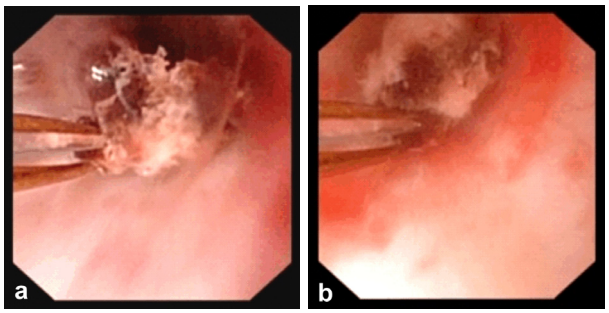

Figure 2 – ***pTa pyelic (a) and caliceal (b) tumor biopsies with the grasping forceps.***

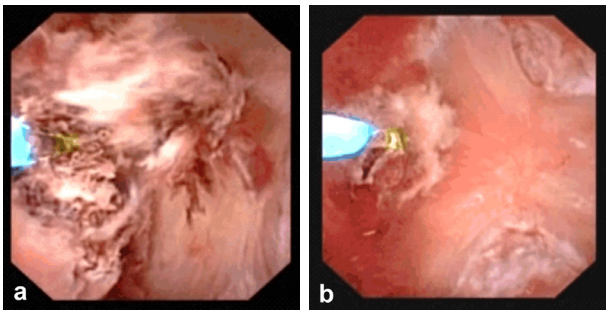

Figure 3 – ***pTa pyelic (a) and caliceal (b) tumors treated by holmium laser vaporization.***

In order to ensure complete objectivity of the evaluation, all the obtained specimens were analyzed by a pathologist with experience in the field of urothelial cancer, blinded to the type of endoscopic visualization leading to the discovery of each presumable tumor. The diagnostic accuracy of the technique was established by centralizing data concerning the pathologically confirmed UUT-TCC lesions discovered by the two types of ureteroscopy and drawing a parallel to the total number of urothelial cancer lesions as well as cases.

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, IBM, Inc.) 20.0 software. With a statistical significance level set at $p<0.05$, the χ^2 (*chi*)-square test was applied.

All diagnostic and conservative treatment procedures were successfully carried out. From the point of surgical safety, no major complications were encountered secondary to the holmium laser vaporization of urothelial tumors (two cases of postoperative hematuria managed conservatively).

Results

Regarding the viability of the specimens in light of the pathological analysis, it was noted that biopsy specimens were too small to provide a reliable pathological result in 24.1% of the cases, while benign lesions were diagnosed in 4.6% of patients. Consequently, a dependable outcome was outlined gathering a total of 113 UUT-TCC lesions (104 pTa and nine CIS) confirmed by pathology in 62 patients who finally constituted the study group of the trial.

As far as the actual diagnostic accuracy achieved during WL/NBI ureteroscopy was concerned, substantial progresses were underlined while introducing the NBI supplementary findings. As of such, on a tumors' related basis, significantly higher overall upper tract and pTa (Figure 4) tumors' detection rates were determined for NBI ureteroscopy by comparison to the WL evaluation (98.2% *versus* 86.7% and 98.1% *versus* 87.5%, respectively). Despite the rather small number of CIS lesions lacking statistical significance, the NBI mode was virtually confirmed as providing diagnostic superiority over WL (100% *versus* 77.8%, respectively) (Table 1).

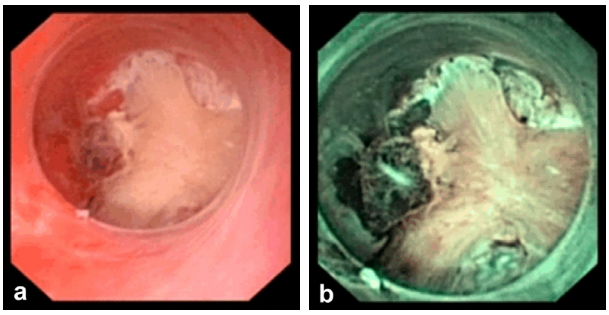

Figure 4 – ***(a and b) Caliceal pTa tumor solely observed when using NBI visualization. NBI: Narrow-band imaging.***

Table 1 – ***Transitional renal cell carcinoma lesions' related detection rates***

Tumors' detection rates	WL–FURS	NBI–FURS	*p*-value
Overall UUT-TCCs (*n*=113)	86.7%	98.2%	<0.05[a]
pTa tumors (*n*=104)	87.5%	98.1%	<0.05[a]
CIS lesions (*n*=9)	77.8%	100%	>0.05[a]
Targeted biopsies' specificity			
Rate of false-positive results	10.1%	17.5%	<0.05[a]

WL: White light; FURS: Flexible ureteroscopy; NBI: Narrow-band imaging; UUT-TCC: Upper urinary tract transitional cell carcinomas; CIS: Carcinoma *in situ*; [a]*Chi*-square test.

Furthermore, the patients' detection rate was significantly improved in NBI mode when compared to standard FURS (98.4% *versus* 91.9%, respectively) due to cases either exclusively diagnosed with UUT-TCC (8.1%) or presenting additional urothelial tumors (12.9%). Overall, a total of 13 pTa (Figure 4) and two CIS lesions (Figure 5) were missed in during the WL examination of the pyelocaliceal mucosa and solely observed in NBI vision mode (Table 2).

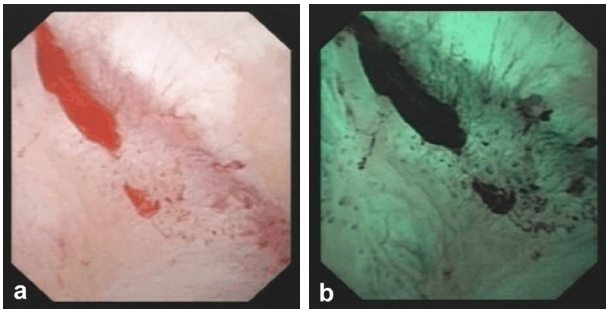

Figure 5 – ***(a and b) Pyelic CIS lesion only emphasized in NBI mode. CIS: Carcinoma in situ; NBI: Narrow-band imaging.***

Table 2 – ***Patients' related diagnostic accuracy***

Patients' reported outcomes	WL–FURS (*n*=62)	NBI–FURS (*n*=62)	*p*-value
Overall UUT-TCC cases' detection rate	91.9%	98.4%	<0.05[a]
Vision mode specific supplementary findings			
Exclusive urothelial carcinoma diagnostic	1.6%	8.1%	<0.05[a]
Additional renal transitional cell lesions	1.6%	12.9%	<0.05[a]

WL: White light; FURS: Flexible ureteroscopy; NBI: Narrow-band imaging; UUT-TCC: Upper urinary tract transitional cell carcinoma; CIS: Carcinoma *in situ*; [a]*Chi*-square test.

On the other hand, NBI-assisted digital FURS was characterized by a significantly increased proportion of unnecessary biopsies being taken by comparison to conventional WL flexible endoscopy, as shown by the significantly elevated rate of false-positive results emphasized in light of the pathological analysis (17.5% *versus* 10.1%, respectively) (Table 2).

Pathology findings

Due to the various difficulties and limitations encountered while attempting to provide a reliable pathological exam when conservatively approaching UUT lesions, we described in this section several cases exemplifying the most frequently observed pathology aspects observed when analyzing specimens obtained by grasping forceps' biopsy during FURS for renal transitional cell carcinoma suspicion.

Case No. 1

Small biopsy from a renal pelvis low-grade non-invasive papillary urothelial carcinoma with cautery artifact (Figure 6). The tumor reveals and overall neat appearance, with some little modifications regarding its architectural and cytological aspects, which can be easily identified using scanning magnification. The loss of the polarity of the cell, the nuclear hyperchromasia and the anisonucleosis were moderate, while the enlargement of the nuclei was mild. In this case, the cauterization artifact is present focally within the lamina propria, thus making it difficult to evaluate the invasion in this region. The tumor stage was reported as pTa only by examination of the superficial lamina propria from around the cautery artifact, since there is no muscular layer present in this biopsy specimen.

Case No. 2

Exophytic caliceal low-grade non-invasive papillary urothelial carcinoma (Figure 7). There was observed an exophytic caliceal tumor composed of multiple fibrovascular fused, forked and fragile cores, most of them ordered, some of them crowded and undirected. The biopsy contains sufficient tumor tissue but is superficial and does not include lamina propria or the muscular layer necessary for excluding the presence of invasion. The tumor was considered as pTa stage exclusively based on the absence of malignant invasion into the fibrovascular cores.

Case No. 3

Renal pelvis CIS (Figure 8) – high-grade flat lesion showing pronounced cytological atypia but lacking a papillary configuration. This case displays a large cell type lesion with nuclear pleomorphism. The cells present complete loss of polarity, marked crowding, pleomorphism

and frequent mitoses. The superficial lamina propria is edematous, hypervascular and inflamed.

Case No. 4

Small biopsies from an area of the renal pelvis' urothelium emphasizing reactive proliferative changes – von Brunn nests (Figure 9). The von Brunn nests are infolding of the upper layer of the urothelium into the lamina propria. In this case, the solid nests lost contact with the urothelium surface, becoming isolated within the superficially inflamed lamina propria. The nests are relatively uniform in size and shape and lack cytological atypia. The absence of deep lamina propria tissue and muscular layer prevent a reliable exclusion of an infiltrative tumor.

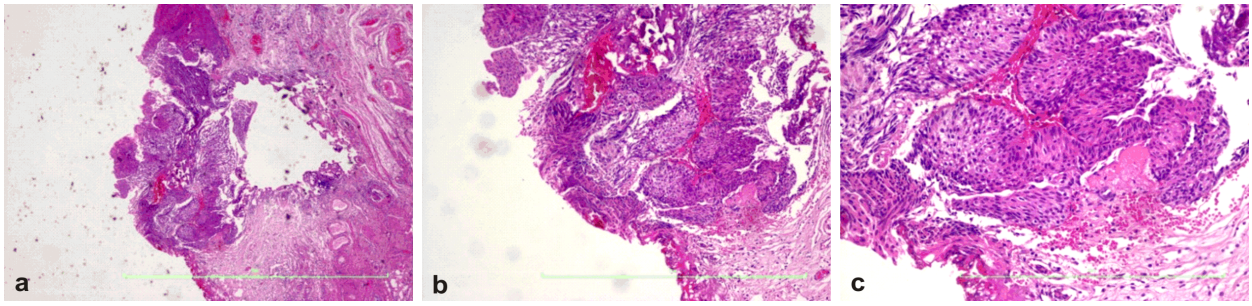

Figure 6 – ***Pyelic low-grade non-invasive papillary urothelial carcinoma (pTaG2): (a) Small pTaG2 tumor with cautery artifact; (b) Minimal variability of architectural appearance; (c) Moderate loss of cell polarity, moderate nuclear hyperchromasia and moderate anisonucleosis. Hematoxylin–Eosin (HE) staining: (a) ×40; (b) ×100; (c) ×200.***

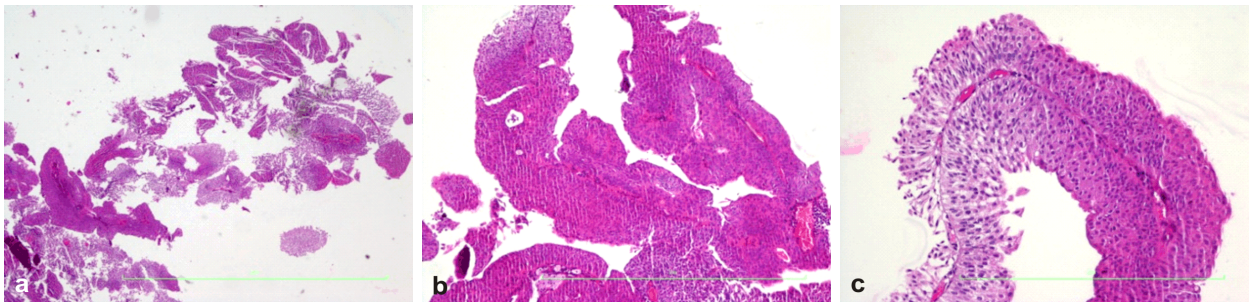

Figure 7 – ***Caliceal low-grade non-invasive papillary urothelial carcinoma (pTaG2): (a) pTaG2 tumor with multiple fibrovascular cores fused, branching and delicate; (b) Minimal crowding and minimal lost of polarity; (c) Moderate loss of cell polarity, moderate nuclear hyperchromasia and moderate anisonucleosis. HE staining: (a) ×40; (b) ×100; (c) ×200.***

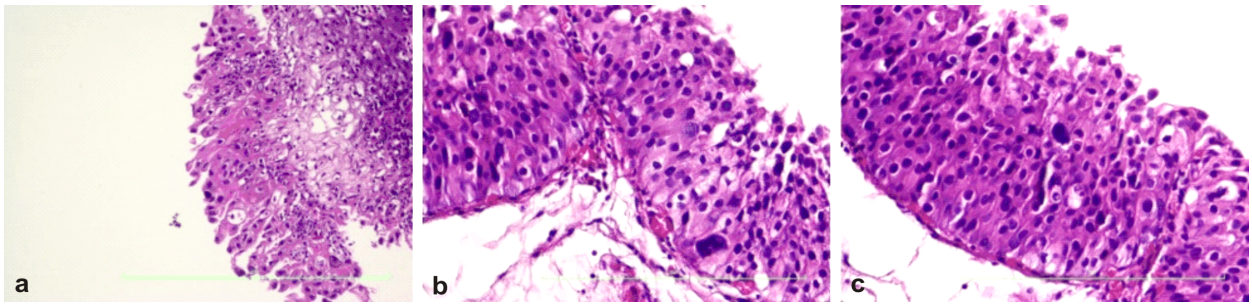

Figure 8 – ***Renal pelvis CIS: (a) CIS lesion showing pronounced cytological atypia, marked disorganization of cells and lacking a papillary configuration; (b) High nuclear/cytoplasmic ratio, nuclear pleomorphism, atypical mitotic figures; (c) Large cell type with nuclear pleomorphism. HE staining: (a) ×200; (b and c) ×400. CIS: Carcinoma in situ.***

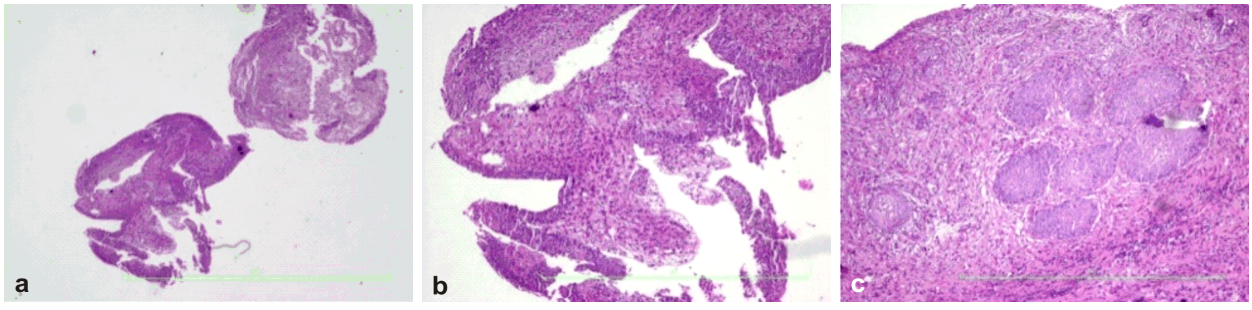

Figure 9 – ***Reactive proliferative change (von Brunn nests; proliferative pyelitis): (a) Pyelic mucosa biopsy; (b) Lamina propria with benign urothelium; (c) Solid nests of benign appearing urothelium that lost continuity with the surface, becoming isolated within the superficially inflamed lamina propria. Such proliferative changes may mimic the nested variant of urothelial carcinoma but do not constitute premalignant lesions. HE staining: (a) ×40; (b) ×100; (c) ×200.***

Discussions

Several major issues impair the diagnostic accuracy in upper tract urothelial carcinoma. Imagery is insufficient to discover small lesions of the pyelocaliceal mucosa and endoscopy becomes imperative while attempting to identify UUT-TCC tumors at an early stage [18]. Digital technology introduces the benefits of superior image quality but WL visualization remains steps away from reliability when dealing with small size papillary or flat CIS lesions [19]. Optical image enhancement technology has been so far supported by the literature data as adding useful abilities to detect malignant changes in the urinary tract mucosa [20].

NBI enjoys the benefits of additional diagnostic information in cases of urothelial non-invasive cancer without the drawbacks of additional costs [21]. NBI has already been confirmed as improving detection of superficial bladder tumors as a substantial proportion of cases are better evaluated when using this vision mode [22]. UUT malignancies constitute an area of interest suitable for NBI endoscopic determinations due to progresses offered by digital FURS incorporating the NBI concept within the same setup [23]. Although already acknowledged as a feasible investigation approach in UUT-TCC, NBI-assisted FURS continues to lack sufficient evidence supporting actual differences in detection rates when compared to the WL digital exploration of the pyelocaliceal system [24].

In any case, some figures do exist among the published reports and an evidence-based parallel with the present study may be considered useful. As of such, there seems to clearly be a well-defined category of patients in which additional urothelial non-invasive malignancies are discovered with the help of NBI technology (25.9% in the literature [17] and 21% in the current trial). Despite relatively remote variations regarding the proportions of cases exclusively diagnosed with UUT-TCC due to the use of NBI (9.5% [17] and 8.1%, respectively) or displaying additional tumors (9.5% [17] and 12.9%, respectively), the idea remains that NBI helps the urologist find more transitional renal cell carcinoma cases as well as lesions.

On a tumors related basis, clinical evidence exists according to the available data that a substantial category of UUT-TCC lesions are identified in NBI mode alone (14.2% [18]). The present study substantiated a similar perspective in light of the 13.3% rate of supplementary CIS and pTa tumors being solely found while applying NBI vision. When referring to the subject of newly diagnosed urothelial carcinoma upon first clinical suspicion, the proportion of cases with non-invasive pTa tumors missed during the WL examination of the upper tract mucosa and only identified in NBI remains important, both according to the previously published articles as well as to this trial (15% [18] and 12.5%, respectively).

On the other hand, one of the most important drawbacks during UUT-TCC diagnostic by means of conservative approach is represented by the often-poor quality of the specimens obtained by performing grasping forceps' biopsies during FURS. More precisely, both according to literature reports [18] as well as to the present study, such specimens are small do not usually include muscular fibers, thus leaving doubts with regard to tumor staging evaluation. From another perspective, the previously published data on the subject underlined the predictive value of tumor grade to be relatively just as relevant as staging in upper tract urothelial carcinoma cases, thus establishing pathology evidence on this basis to be sufficient [19].

However, it is not infrequent among situations in the daily practice that samples taken using the grasping forceps from the pyelocaliceal mucosa during FURS provide insufficient bioptic material for a conclusive pathological analysis to be performed. It is a reality supported both by previously known reports (26% [18]) as well as by the presently described series (24.1% of the enrolled cases). Given the small size of the grasper taking biopsy specimens as well as the reduced caliber of the working channel of the flexible ureteroscope through which samples must be retrieved, it is clear that limitations in terms of accurate pathology reside from practical drawbacks and will continue to do so in the foreseeable future [25].

From another point of view, it is quite commonly acknowledged that a higher sensitivity comes along with a greater chance of taking a larger proportion of unnecessary biopsies. In the field of upper tract urothelial carcinoma, the literature findings hardly addressed the issue of false-positive results related to NBI-guided biopsies. However, the NBI-based non-muscle invasive bladder cancer diagnostic has been more thoroughly documented and confirmed the substantially elevated frequency of unconfirmed malignant lesions when drawing a parallel to the classical WL endoscopy (31.6–36% *versus* 24.5–33%, respectively) [26–28]. Expectantly so given the profile of UUT-TCC, at smaller numbers, NBI-suspected lesions during digital FURS confirmed the lower specificity when compared to the WL endoscopy (17.5% *versus* 10.1%, respectively).

Given all of the above, it becomes clear that, on one hand, NBI defines itself as a useful tool during FURS, while on the other, much more scientific support is required before reliably establishing the actual role of NBI in UUT-TCC daily management [13].

Based on the current findings, it has been emphasized on an evidence-based support that, as additional tool for the standard WL evaluation of the pyelocaliceal system urothelium, NBI-guided biopsies provide a significant diagnostic improvement during digital FURS.

Conclusions

Although NBI as an additional diagnostic method has been introduced as a modality to enhance the bladder tumors' diagnostic accuracy, very few data are available in the published literature concerning the UUT carcinomas. The originality of the current report resides in providing evidence-based arguments in support of the diagnostic advantages of NBI during UUT-TCC endoscopic assessment. Changes in terms of diagnostic accuracy for newly discovered cases of upper tract urothelial carcinoma substantiated a significant proportion of additional UUT-TCC tumors as well as patients being found in NBI mode at the cost of decreased specificity. Despite shortcomings in terms of biopsy specimens' quality and tumor staging' reliability, practically unavoidable due to the technically-related FURS limitations, a substantial category of pTa and CIS lesions were solely detected and subsequently

vaporized due to the use of NBI. Therefore, at basically no additional cost, an improved conservative cancer management becomes possible due to a superior digital endoscopic visualization of the pyelocaliceal mucosa through optical image enhancement technology.

Conflict of interests

The authors declare that they have no conflict of interests.

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