THE UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
THE FIELD OF MEDICINE

DIGITAL FLEXIBLE URETEROSCOPY ASSISTED IN NBI AND HOLMIUM LASER VAPORATION IN TRANSITIONAL CARCINOMA OF THE UPPER URINARY TRACT

SUMMARY OF THE DOCTORAL THESES

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List of published scientific papers

1. **Iordache VF**, Geavlete PA, Georgescu DA, Ene CV, Păunescu MA, Niculae A, Peride I, Neagu TP, Bulai CA, Bălan GX, Geavlete BF, Lascăr I. NBI-assisted digital flexible ureteroscopy in transitional renal cell carcinoma - an evidence-based assessment "through the looking glass" of the pathological analysis. Rom J Morphol Embryol. 2018;59(4):1091-1096. PMID: 30845289. Factor impact: 0.833

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2. **V. Iordache**, R. Multescu, B. Geavlete, L. Chiperi, P. Geavlete, Narrow Band Imaging and Holmium Laser Photoablation in Upper Urinary Tract Tumor Conservative Management - An Update, Revista Romana de Urologie Vol. 18, Nr.3 anul 2019

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3. Geavlete B, Popescu R, **Iordache V**, Geavlete P. Single-Use vs Reusable Ureteroscopes in Horseshoe Kidney Stones. Maedica (Bucur). 2021 Dec;16(4):568-573. doi: 10.26574/maedica.2021.16.4.568. PMID: 35261654; PMCID: PMC8897789. Factor de impact: 0,67

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4. PM.1.1. “Tips and trick” în prezervarea ureteroscoapelor flexibile până la 270 de proceduri Tips and tricks for preserving the digital flexible ureteroscope for up to 270 interventions B. Geavlete, D. Georgescu1 R. Multescu, C. Ene, **V. Iordache**, P. Geavlete. Al 34-lea Congres al Asociației Romane de Urologie. ROMURO 2018

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6. The outcomes of the digital flexible ureteroscopy in multiple renal calculi Geavlete B., Multescu R., Georgescu D., **Iordache V**., Ene C., Ene M.A., Geavlete P.A. (Bucharest, Romania). EAU 17 ch Central European Meeting (CEM) in conjunction with conference of the Czech Urologycal Society. 19-20 October 2017, Plzen, Czech Republic

7. How can we protect flexible ureteroscope: Tips and tricks Stan M., **Iordache V**., Geavlete B., Multescu R., Geavlete P.A. (Bucharest, Romania). EAU 17 ch Central European Meeting (CEM) in conjunction with conference of the Czech Urologycal Society. 19-20 October 2017, Plzen, Czech Republic

List of abbreviations

UTUC – Upper Tract Urothelial Carcinoma

NBI - Narrowband Image

fURS - Flexible ureteroscopy

BCG – Vaccine name comes from the bacillus Calmette–Guérin

WHO - World Health Organization

EAU – European Urology Guide

IVU - Intravenous urography

CT - Computed Tomography

MRI - Magnetic Resonance Imagining

PN - Partial Nephrectomy

CCD - Color Chip Device

WLI - White Light Imaging

UC - Urothelial Carcinoma

PC TCC – Pyelocaliceal Transitional Cell Carcinoma

1.Introduction

The history of medicine records a continuous evolution of imaging and treatment methods, technology being an important part of modern medicine. Urology has always been one of the surgical branches that enthusiastically adopted technology to support the patient.

Since the introduction of the first cystoscope, urology has been at the forefront of endoscopic use in clinical practice. Endoscopy is used in both diagnosis and therapy.

The development and miniaturization of optical and endoscopic systems led to the development of minimally invasive surgical procedures that over time replaced traditional surgery.

The field of ureteroscopy has acquired a continuous evolution since the first ureteroscopes were introduced. In the past 10 years, we have entered the digital age of ureteroscopy and semi-rigid and flexible ureteroscope options have become available. Recently, flexible ureteroscopes have been built with digital imaging chips [1].

According to the EAU guidelines, it is recommended to use flexible ureteroscopes instead of rigid ones [2].

The development of the flexible ureteroscope (FURS) has provided major diagnostic and treatment advantages for most upper urinary tract pathologies [3]. Small diameter flexible ureteroscopes are effective for diagnosing and treating upper urinary tract pathology [4].

Optical image enhancement technology has so far been supported by literature data as adding useful abilities to detect malignant changes in the urinary tract mucosa[5].

When performing ureteroscopy for the diagnosis and treatment of upper tract urothelial tumors, the risk of trauma to the upper urinary tract should be minimized [6]. The advent of thinner instruments for flexible ureteroscopy (FURS) with digital technology has improved the diagnostic value of ureteroscopy. The use of image enhancement techniques during URS, namely NBI narrowband imaging can improve the detection of urothelial tumors [7].

Compared with WLI, flexible ureteroscopy in NBI provided a better image of UTUC especially of the border zone between tumor tissue and normal tissue. NBI improved the detection of UTUC over the standard WLI method with a higher diagnostic rate. NBI helps find additional tumors and better characterize those identified to eradicate tumor tissue**[12].**

Given the natural history of UTUC, its potentially aggressive clinical course, and the consequent rigorous follow-up recommendations, there is a direction toward advanced technologies to optimize cancer detection and treatment [8]. In cases with a solitary kidney or in cases of chronic renal failure, organ preservation is crucial and conservative approaches are indicated [9]. NBI is an optical image enhancement technology designed to enhance contrast between mucosal and microvascular structures without the use of dyes. The flexible laser fiber is used and tumor ablation is performed by laser vaporization. It is used in contact with the tissue, determining an excellent hemostasis and does not cause ureteral strictures which are a frequent complication for electrocautery. Urologists should take into account the clinical specificity, the characteristics of each patient to determine the optimal treatment regimen, to treat these tumors [10].

Given the relatively small size of the sampling device used to obtain biopsy specimens, as well as the small caliber of the working channel of the flexible ureteroscope through which the specimens must be extracted, it is clear that the limitations in pathology originate precisely in from the practical disadvantages of the limitation of the standard instrument used, having the same predictability in the future [11]. Based on the current findings, the important adjunctive role in the detection of urothelial carcinoma of the pyelocalyceal system to flexible ureteroscopy-guided biopsies using NBI visualization by comparative terms of the standard WL method was emphasized on an evidence-based basis..**[13]**

NBI is noted to be a feasible method. The results of other similar studies will confirm whether, in the long term, this technique improves the proportion of favorable results for the treatment of high urothelial tumors. Most of the studies involved in this field have reflected promising results regarding the viability of cystoscopy in the NBI mode. However, speaking objectively, future works will be necessary, well argued on systematic analyses, which will demonstrate, without a doubt, the superiority of the new method over the standard approach.

The trend of modern urology is very clearly highlighted by most of the works published in the specialized literature in recent years through the endoscopic approach of the upper urinary tract for a rather varied pathology.

2. Objectives of the study

The aim of this study is to analyze the diagnostic variant of pyelocaliceal urothelial tumors by flexible ureteroscopy (retrograde intrarenal surgery), using white light (WL) and the Narrow Band Imaging (NBI) technique as visualization method. The study hypothesis was, therefore, that with this new visualization technique, flexible ureteroscopy with NBI visualization is superior to the classical variant for visualization of PC-TCC intrarenal urothelial carcinoma lesions, both for single and additional lesions viewed in WL.

The study carried out is a prospective, observational analytical one, the patients whose data were recorded and analyzed were hospitalized in the Urology clinic of the Saint John Emergency Clinical Hospital in Bucharest, during the period 2014-2018.

The registration, preoperative evaluation and surgical treatment of the patients that make up the result of this work were performed in this clinic, by urologists.

The structure of the study is as follows:

A second stage was represented by the biopsy of these lesions with forceps. Each tissue sample collected was anatomopathological analyzed.

Regarding the actual cancer-specific treatment, all lesions were treated in a third stage conservatively, by Holmium:YAG laser vaporization with a 275 μm laser fiber. As the final step of the digital URS-F procedure, a final WL and NBI control was applied to all targeted mucosal areas, looking for any residual tumors/margins. Although rarely necessary, laser coagulation of potentially existing bleeding sources was carefully applied.

As a safety measure, a JJ stent was placed in each case at the end of the procedure.

In the second part, patients with PC-TCC treated by this conservative procedure were evaluated for a period of 3 years and compared with a similar group in which flexible ureteroscopy diagnosis and laser ablation of tumors were performed only in WL.

The following stages were followed throughout the conduct of this study:

Implementation of a work performance protocol;

Obtaining an Informed Consent from each patient, strictly respecting the criteria of professional ethics and data confidentiality;

Selection of patients respecting both inclusion and exclusion criteria;

Collection of work data useful for realizing the study hypothesis;

Statistical analysis of all data.

3. Study hypothesis

Transitional cell carcinomas represent the majority of upper urinary tract tumors (UUT-TCC). The factors predisposing to the formation of these neoplasms are heterogeneous - environmental factors, heredity, hormonal changes. It is a malignancy with a low prevalence, but it is frequently multifocal, being usually diagnosed at an advanced stage with multiple complications related to impaired renal function, or it may become more complicated during the evolution of patients with chronic renal failure, and often makes their perioperative management very difficult patients. Although it is recognized as a safe and feasible diagnostic method by the European Association of Urology in PC-TCC type neoplasias, being described in the European Guideline of Urology, F-URS assisted by NBI visualization continues to lack sufficient strong evidence to support real differences in the detection rates of these tumor types.

We proposed that, by comparing the two diagnostic methods, we would evaluate patients from our clinic in order to compare the identification rates of these malignancies through the two visualization methods.

The therapeutic options for these types of tumors are:

- Conservative treatment, in this category entering the retrograde flexible ureteroscopic approach (WL or NBI), possibly with tumor laser vaporization
- Radical nephroureterectomy

All these options are accepted by international specialist forums and each one presents multiple advantages and disadvantages.

Conservative methods are especially suitable for tumors in an early stage and for patients in whom radical treatment can have significant consequences: patients with a single kidney, patients with bilateral tumors, patients with pre-existing renal failure, patients with a physical status that does not allow a major surgery etc.

The impact of visualization in NBI on treatment effectiveness will also be tracked.

The hypothesis of the study is that the use of NBI improves the diagnostic identification of PC-TCC and optimizes the conservative treatment - laser ablation by retrograde flexible ureteroscopic approach.

4. The general methodology of the study

4.1 Data recorded

The record of each evaluated patient includes both medical data and personal data recorded following their evaluation

4.2 Criteria for inclusion and exclusion of patients in the study

Inclusion criteria:

- patients over 18 years of age;
- patients with a physical status predicting a life expectancy greater than 5 years;
- patients who, in the event of the diagnosis of a tumor lesion at the level of the upper urinary tract, have an indication for conservative surgical treatment: single kidney, chronic renal failure;
- suggestive elements for the presence of a urothelial tumor lesion at the level of the upper urinary tract: filling defects of the pyelocaliceal system according to the results of computed tomography (CT), unilateral hematuria during cystoscopy or suspiciously malignant urinary cytology.

Exclusion criteria:

- Age of patients under 18 years;
- CT aspects suggestive of invasive lesions in the upper urinary tract;
- The presence of urothelial tumors at the ureteral level;
- Patients who refuse conservative surgical treatment of urothelial tumors of the upper urinary tract;
- Biopsy specimen with too small an amount of tissue to allow an optimal anatomic-pathological examination;
- The presence of only benign lesions at the anatomical-pathological examination;
- The presence of tumor lesions larger than 2 cm;
- Radical cystectomy in the antecedents for bladder tumors;

In the second part of the study, patients eligible for the full completion of the first stage and who accept and undertake a follow-up of at least 3 years will be included.

The study was divided into two stages:

Stage I: diagnosis of malignant lesions using NBI vs WL technology

Stage II: follow-up of relapses in patients who were diagnosed using NBI and conservative treatment compared to patients with nephroureterectomy.

THE IMPACT OF NBI-ASSISTED VISUALIZATION ON THE ACCURACY OF INTRAOPERATIVE IDENTIFICATION AND SURGICAL TREATMENT OF PIELO-CALYCEAL UROTHELIAL CARCINOMAS THROUGH FLEXIBLE URETEROSCOPY AND LASER VAPORIZATION.

5. Stage I of study

Stage I: diagnosis of malignant lesions using NBI vs WL technology.

5.1 Material and method

The study followed the implications of the clinical manifestations of the patients in the choice of treatment modality, the moment of the intervention, as well as on the operative technique, the results and complications of endoscopic interventions.

Endoscopic evaluation

Cystoscopic evaluation should be a routine examination in patients with suspected high urothelial tumor because they have a 20% to 48% risk of developing synchronous or metachronous bladder tumors. The analysis allows excluding the presence of tumors in the bladder and urethra, especially in the complementary use of fluorescence techniques. Also, the endoscopic evaluation allows retrograde uretropyelography to be performed.

Flexible ureteroscopy allows visualization and biopsy of lesions in the pyelocalyceal system and ureters, as well as urine collection for cytological examination. This endoscopic method offers advantages especially in patients with uncertain diagnosis or in cases where conservative therapy is intended.

Cystoscopy evaluation, diagnosis, biopsy and eventual complete resection of tumors or their laser vaporization, transform ureteropyelonephroscopy from a diagnostic method into a therapeutic method. All these diagnostic and therapeutic stages are usually carried out within a single intervention, the technique of which we will describe in the following pages.

The histopathological examination of the tissue collected either by endoscopic biopsy or by brushing biopsy of high urothelial lesions, is the one that makes the diagnosis

certain. Endoscopic biopsy, performed with the help of the flexible ureteroscope, increased the accuracy of the diagnosis of high urothelial tumors but also the risk of perforation of the upper urinary tract.

In order to ensure the complete objectivity of the evaluation, all specimens obtained were analyzed by two different anatomopathologists, with extensive experience in the field of urothelial cancer, analyzing "blindly" to the type of endoscopic visualization that led to the discovery of each suspected tumor.

In case of conflicting diagnoses, a third pathologist was called to reevaluate the samples. To address the issue of interobserver variability, questionable cases were viewed at the weekly Department of Pathology Committee.

Surgical technique

Patient position. All patients were placed in the standard lithotomy position

Cystoscopy and providing access to the upper urinary tract. The first operative time was represented by the careful inspection of the urinary bladder, in order to identify possible urothelial tumor lesions at this level. The identification of any potentially tumoral lesion at this level made the patient ineligible for the present study.

Dilation of the ureteral orifice was performed with conical dilators with progressively increasing diameters, from 6F to 10F.

Semi-rigid ureteroscopy. The next operative stage was the inspection with a Storz 9F semi-rigid ureteroscope of the ureter, up to the level of the uretero-peliac junction.

Installing the ureteral access sheath. A Cook Flexor 10/12F ureteral access sheath was successfully fitted in all cases. This was slid over the previously placed Lunderquist guide under fluoroscopic control

Flexible ureteroscope inspection. Reaching the renal level, under optical and possibly fluoroscopic control, the collecting system was explored with the flexible ureteroscope starting with the basin, then the upper calyceal group, then the middle calyceal group and, finally, the lower calyceal group

Initially, the inspection was carried out in white light. When a suspicious lesion was identified, repeated switching between white light and NBI imaging mode was continued.

NBI is a patented optical filter technology for the diagnosis and treatment of high urothelial tumors, generating significantly higher contrast between blood vessels and surrounding tissue than white light (WL) imaging.

The way NBI works is this: when WL hits the surface of a tissue, all colors are absorbed; in contrast, NBI uses only blue and green light. When blue light and green light reach the surface of the tissue, they are absorbed by the hemoglobin in the blood vessels. The blue and green light of NBI penetrate the tissue layers differently.

While the blue light is absorbed by the capillaries in the mucosa, the green light reaches deeper into the submucosal area, where it is reflected by the blood vessels. This is why NBI creates a significantly higher contrast between blood vessels and surrounding tissue than WL. The degree of light absorption depends on the wavelength. Blue light with a wavelength of 415 nm and green light with a wavelength of 540 nm are strongly absorbed by hemoglobin in blood vessels. Since small tumors are often surrounded by a large number of blood vessels, NBI helps to detect them at an early stage and analyze these areas accordingly.

As NBI is a purely optical system, it does not require any installation or active substances administered by any route beforehand, and therefore requires no preparation time being available directly with Olympus systems.

If the lesion was visible only in white light, it was marked on a map of the pyelocalyceal system, and if it was also visible in NBI, it was marked on a second map. At the end of the white light inspection, a new inspection was carried out only in NBI, with the identification of lesions visible only in this mode of visualization. The latter were marked on a third map.

The optical zoom offers a new visualization, better than before, of the epithelial ridges on the surface and a better interpretation of the color changes that appear, through morphological analysis of the superficial vascular network, which is always altered due to tumor angiogenesis.

When the zoom is activated, the focal distance between the objective and the surface of the mucosa decreases proportionally to the image magnification power, and for this the tip of the instrument is placed a few millimeters approximately 3 mm from the surface, and a small area of the mucosa is explored.

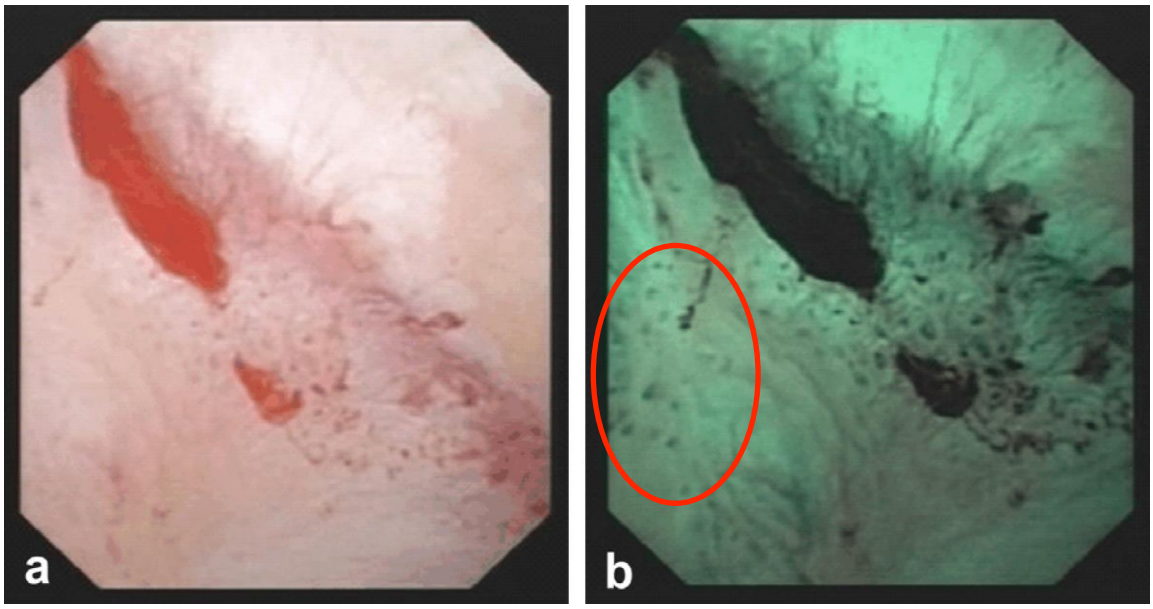

Figura 5.9. *Suspicious additional skin lesion, visible only in NBI (b)*

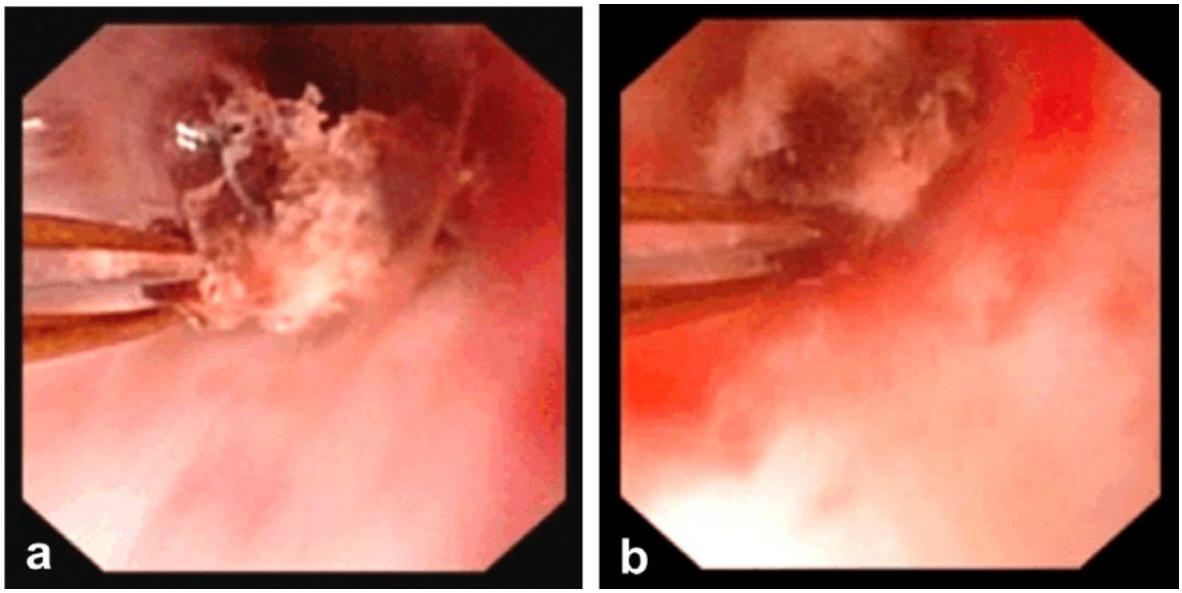

Figura 5.11 *Cold forceps biopsy of suspicious skin (a) and calyceal (b) lesions*

After making the three maps (lesions visible only in white light, lesions visible in both visualization modes, respectively lesions visible only in NBI), they continued with their biopsy with "cold" forceps. In all cases an attempt was made to sample as much tissue as possible. Not all harvested biopsies had a sufficient amount of tissue to allow an optimal histopathological examination; these cases were excluded from the study.

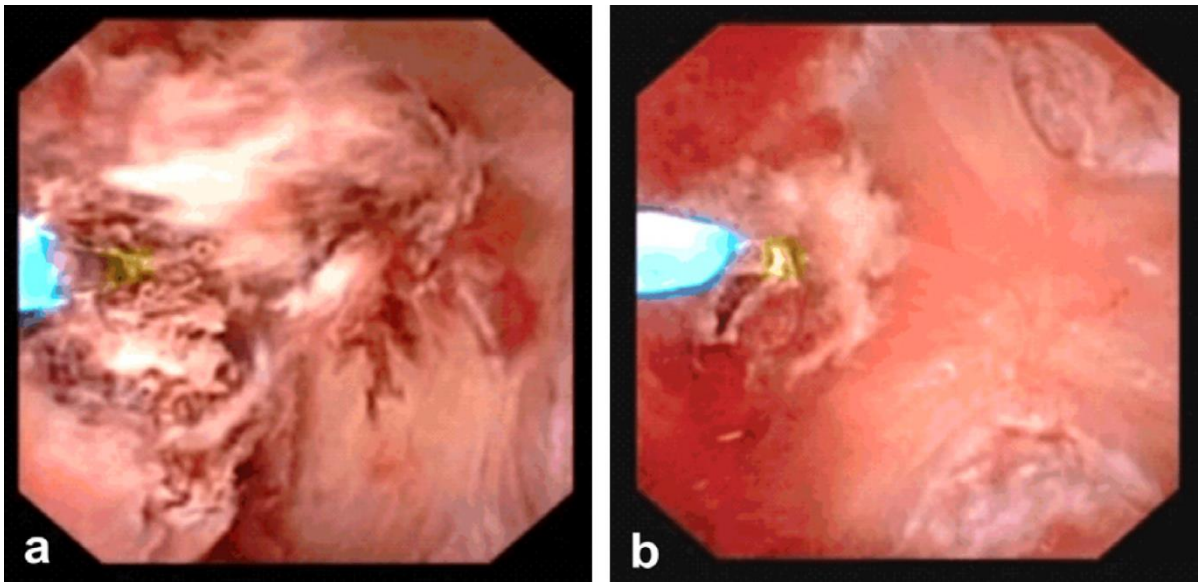

Figura 5.12 *Laser vaporization of some pTa tumor formations at the skin level (a) and lower calyceal level (b)*

The next stage was the laser vaporization of the tumor tissue. In all cases the 275 micron fiber was used, the settings being represented by frequencies of 10-12 Hertz and energy of 0.8-1 Joule, with powers of 10-12 watts. After the destruction of the tumor tissue until in macroscopically healthy tissue, thorough laser coagulation of bleeding sources was practiced.

At the end of the intervention, a new inspection in white light and NBI was performed to identify possible areas of remaining tumor tissue (isolated or at the edge of the tumor bed).

At the end of the intervention, in all cases, a JJ Ch 7/ 26 or 28 cm stent was placed. The hydrophilic guide was inserted over the flexible ureteroscope up to the pyelo-calyceal level and held at this level while the endoscope en bloc with the ureteral access sheath was withdrawn.

The purpose of withdrawing the endoscope en bloc with the access sheath is to allow a final inspection of the ureter, to identify possible injuries at this level.

5.2 Statistical analysis

The precision diagnosis of the technique was established by centralizing the data on the anatomopathological confirmed UUT-TCC of the lesion discovered by the two types of ureteroscopy, making a parallel with the total number of urothelial neoplasia lesions.

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

5.3 Results

A total of 87 patients were initially enrolled in this study. Of these, in terms of the quality of the biopsy specimens collected (in the sense of obtaining a sufficient amount of tissue to allow optimal evaluation by pathologists), it was noted that they were too small to provide a reliable pathological result in 21 cases, representing 24.1% of cases. Also, exclusively benign lesions were diagnosed in 3 patients, representing 4.6% of cases.

Both categories of patients were excluded from the analysis. Consequently, a reliable result was outlined in 62 eligible patients, who finally constituted the study group. A total of 113 UUT-TCC lesions were identified in these patients. In terms of tumor type, 104 were pTa lesions and 9 were CIS lesions.

Regarding the number of cases diagnosed by different visualization modes, 56 cases showed lesions visible in both WL and NBI, lesions visible only in WL in one case, and lesions visible only in NBI in 5 cases.

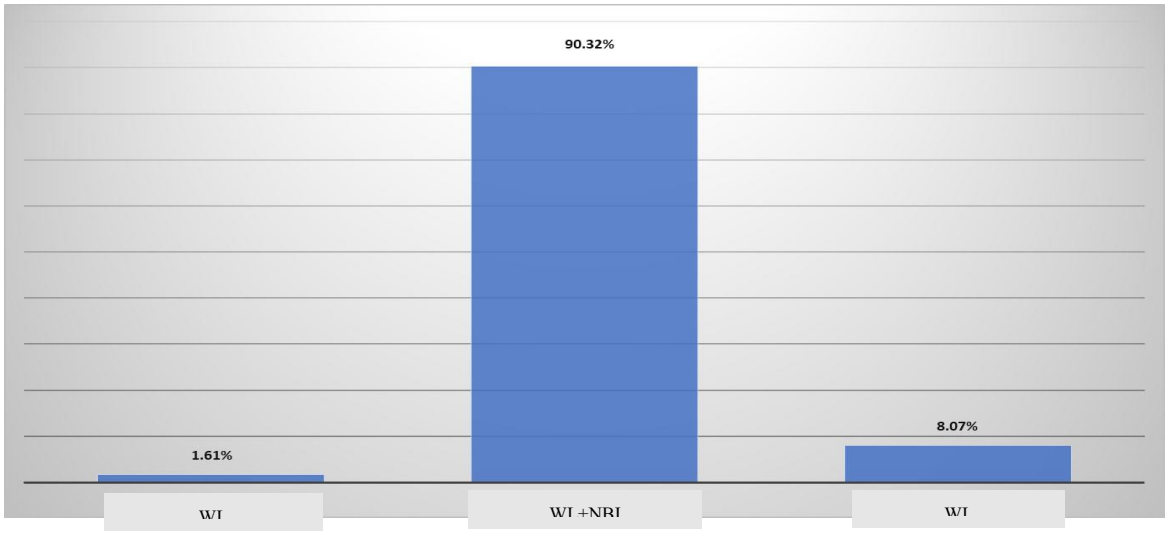

Figura 5.16 *Distribution of cases according to the type of visualization that identified the tumor lesions*

Considering the total number of malignant lesions visualized by the different detection modes, a number of 96 lesions were visible in WL and NBI, only in WL a number of 2

lesions, and exclusively by NBI a number of 15 lesions. Of the 96 lesions visible in both WL and NBI, 89 were pTa lesions and 7 lesions were CIS. Both lesions identified only in WL were pTa. 13 lesions visualized only in NBI were pTa and 2 lesions were CIS.

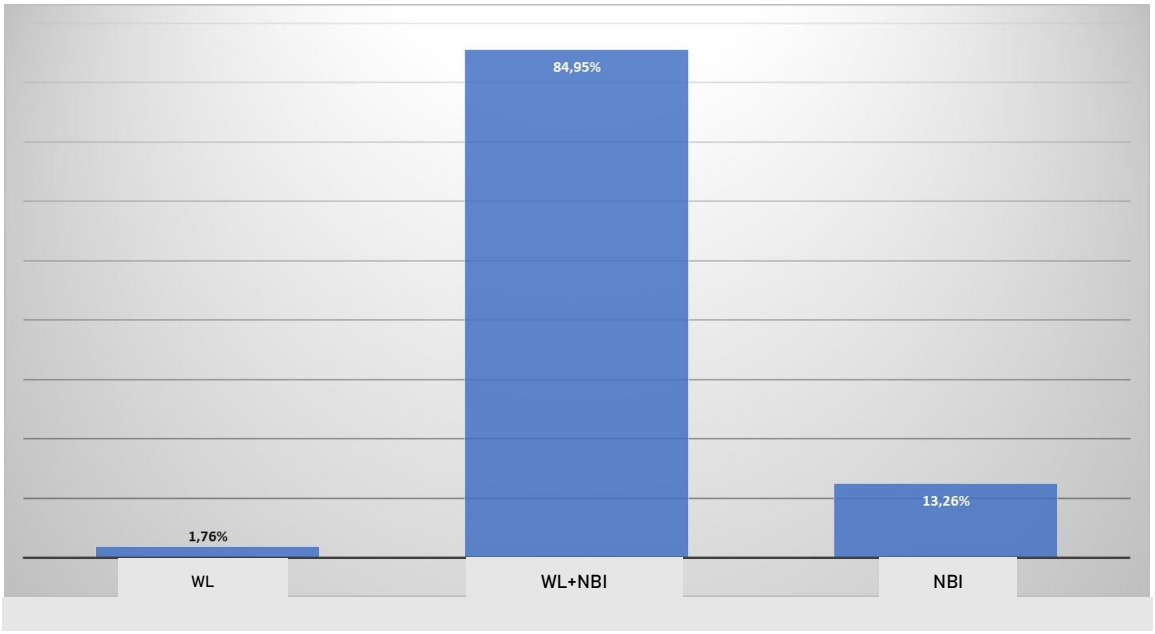

Figura 5.17 Distribution of tumor lesions according to visualization type

Regarding the identification of tumor lesions, detection rates were significantly higher for ureteroscopy combined with visualization in NBI compared to evaluation in WL alone, for both all and pTa type lesions.

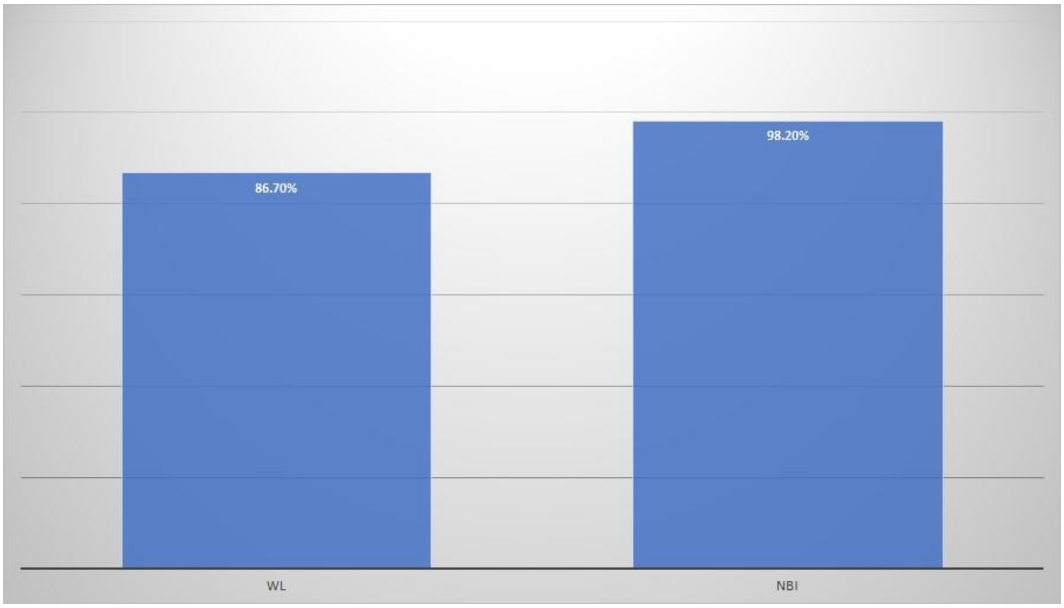

Figura 5.20 Global detection rate of tumor lesions by visualization type

Thus, the overall detection rate of malignant lesions was 98.2% for visualization in NBI versus 86.7% for visualization in WL, respectively a detection rate of pTa lesions of 98.1% for visualization in NBI versus 87 .5% for viewing in WL (both differences having statistical significance).

Despite the rather small number of CIS lesions (thus leading to a lack of statistical significance), the NBI mode was virtually confirmed to provide diagnostic superiority (100% of cases) compared to the standard WL method (which presented an accuracy of 77.8%).

In addition, the detection rate of patients with confirmed neoplasia was statistically significantly improved in NBI mode compared to standard URS-F in WL (98.4% vs. 91.9%). The association of visualization in NBI proved superior both in terms of newly diagnosed cases of UUT-TCC (8.1%) or in terms of the identification of additional urothelial tumors (12.9%). Overall, a total of 13 pTa lesions and two CIS lesions were missed during WL examination of the mucosa of the pyolocaliceal system and observed only in the view module using NBI.

Tumor Detection Rate	**F-URS in WL**	**F-URS in NBI**	**p**
Total number of lesions (n = 113)	**86,7%**	**98,2%**	**<0,05**
pTa tumors (n=104)	**87,5%**	**98,1%**	**<0,05**
CIS (n = 9)	**77,8%**	**100%**	**> 0,05**
False positive rate	**10,1%**	**17,5%**	**<0,05**

Figura 5.23 Positive diagnosis accuracy rate per patient

On the other hand, NBI-assisted digital URS-F was characterized by a significantly increased proportion of unnecessary biopsies compared to conventional flexible endoscopy

with white light (WL) visualization, as shown by the significantly increased rate of false positive results, fact confirmed by pathological analysis (17.5% versus 10.1%).

In the case of high urothelial tumors, conservative treatment is usually reserved for patients in whom the presence of a single tumor formation has been identified in a superficial stage or for those in whom radical treatment raises significant risks: patients with a single kidney, bilateral damage, renal insufficiency, or patients with major comorbidities.

The ureteroscopy treatment can be applied to ureteral tumors and does not present the percutaneous treatment risks of dissemination and seeding of the percutaneous approach.

It can usually be performed in the same session as the initial diagnostic ureteroscopy.

The routine use of a ureteral access sheath appears to facilitate flexible ureteroscopy by decreasing operative time and cost, allowing direct visualization of the ureteroscope insertion with simple ureteral reentry and performing interventions with reduced pressure on the pyelo-calyceal system (and consequently an incidence lower potential complications).

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

5.4 Conclusions

NBI appears to represent a valuable diagnostic technology for UUT-TCC urothelial neoplasia, showing considerable improvement in tumor visual accuracy as well as their detection rate. It also allows the urologist to determine the exact boundaries of the tumors with relative ease, thus facilitating the complete vaporization of these tumor formations with the energy provided by the laser fiber.

The anamnesis followed the evaluation of the favorable factors of high urothelial tumors of the elements that contribute to the choice of the therapeutic attitude, as well as to the prediction of the degree of difficulty of the intervention and the occurrence of incidents and complications

The study followed the implications of the clinical manifestations of the patients in the choice of treatment methods, the moment of the intervention, as well as the operative technique, the results and complications of endoscopic interventions.

The biopsies collected intraoperatively were noted to be too small for a proper anatomopathological examination in a quarter of the cases and in very few cases they were benign

The lesions visualized in WL were confirmed by NBI with a significant percentage detected only in NBI

Regarding the identification of tumor lesions, the detection rates were significantly higher for ureteroscopy with associated visualization in NBI compared to evaluation in WL alone.

The overall detection rate of malignant lesions was statistically significantly higher for visualization in NBI compared to lesions visualized in WL.

The detection rate of high urothelial tumors for pTa lesions was higher in techniques using the ureteroscope in NBI compared to those using WL

In the case of cis lesions, the detection rate in NBI was clearly superior to those using light in WL. The detection rate of patients with neoplasia was clearly superior in NBI. No significant complications were registered with the laser vaporization of the tumor formations. All suspicious lesions were biopsied with forceps.

LONG-TERM IMPACT ON THE TREATMENT EFFICIENCY OF PIELO-CALYCEAL UROTHELIAL TUMORS BY NBI-ASSISTED FLEXIBLE RETROGRADE URETEROSCOPY AND LASER VAPORIZATION

6. Stage II of study

Stage II: follow-up of relapses in patients who were diagnosed using NBI and conservative treatment compared to patients with nephroureterectomy.

6.1 Material and method

61 patients who completed the first stage were enrolled in this second stage of the study: the diagnosis with superficial urothelial tumor lesions only at the pyelo-calyceal level, confirmed anatomically-pathologically, treated conservatively by Holmium laser vaporization on the flexible ureteroscope, assisted by NBI. They constituted the study group. One patient who completed the first part of the study refused to participate in the second part, not undertaking a follow-up of at least 3 years (due to relocation to another city). Control patients were identified retrospectively.

6.2 Post-operative follow-up protocol

Monitoring of patients with high urothelial tumors is indicated to detect the occurrence of metachronous bladder tumors, as well as local or distant recurrence. It is recommended to follow up patients at 3-month intervals in the first year after they have been declared "tumor-free" by endoscopic or open methods.

Each patient is followed:

1. *Physical examination, urine cytology* (only for high-risk tumors, with increased grading),

2. *Cystoscopy:* in the first year every three months, in the second and third years every six months; annually thereafter.

3. *UIV/UPR* of the contralateral kidney - annually.

4. *Endoscopy at the level of the ipsilateral urinary tract* (for patients who have undergone conservative interventions): biannually in the first years and annually thereafter.

5. *Metastatic evaluation* required in all patients with a high risk of tumor progression (high grading, infiltrative tumor): physical examination, lung x-ray, liver enzymes: quarterly in the first year, biannually in the 2nd and 3rd year and annually in the 4th and 5th year; evaluation of the urothelium further.

6. *CT/MRI of the abdomen and pelvis:* biannually in the 1st and 2nd year, and annually in the 3rd, 4th and 5th year.

7. *Bone scintigram:* only for symptomatic patients or patients with elevated serum alkaline phosphatase levels.

6.3 Monitored parameters

A first assessment was performed 10 weeks after the intervention to identify and treat patients with residual tumor tissue. Subsequently, the patients in the two groups were evaluated comparatively at 1 and 3 years. Recurrence rates, the rate of patients who underwent nephroureterectomy, and cancer-specific survival were compared.

6.4 Statistical analysis

The statistical study was carried out Statistical Package for the Social Sciences (SPSS, IBM Inc.) 20.0. Student's t-test was applied, with a cut-off value for statistical significance of p of 0.05.

6.5 Results

A first assessment was performed 10 weeks after the intervention to identify and treat patients with residual tumor tissue. Subsequently, the patients in the two groups were evaluated comparatively at 1 and 3 years. Recurrence rates, the rate of patients who underwent nephroureterectomy, and cancer-specific survival were compared.

In the study group, 56 patients presented with low-grade pTa tumors, and 5 patients with high-grade pTa tumors. For this reason, to be part of the control group, consecutive patients with a follow-up of at least 3 years were selected, 56 with low-grade pTa tumors and 5 patients with high-grade pTa tumors.

At 10 weeks, residual tumor tissue was identified by flexible ureteroscopy approach

under white light in 8.2% (5 patients) of the study group, respectively 34.4% (21 patients) of the control group ($p<0.005$). In all these patients, the remaining tumor tissue was re-biopsied and removed by laser ablation. White light inspection was applied to patients in both groups in order not to introduce sources of error into the statistical study.

The relapse rate at 1 year was 3.3% in the study group, respectively 8.2% in the control group ($p<0.05$). Depending on the histological characteristics, at 1 year the relapse rates in the study group were 1.8% in patients with low-grade tumors and 20% in those with high-grade tumors. In the control group, these rates were 7.1%, (statistically significant difference, $p<0.05$), respectively 20% (statistically insignificant).

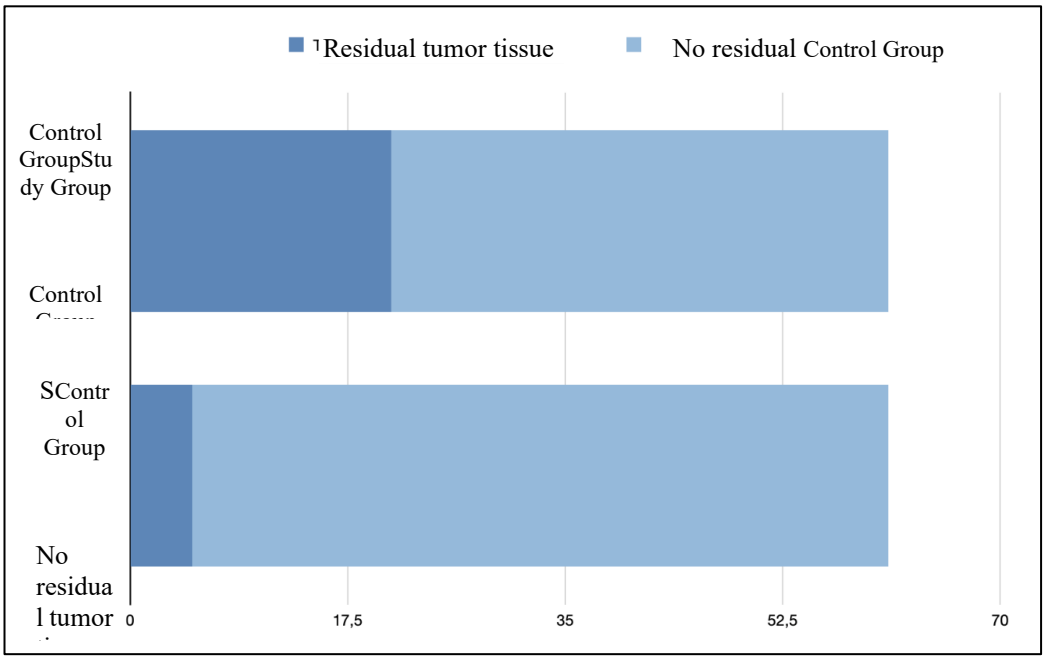

Figure 6.2 The presence of residual tumor tissue 10 weeks after the intervention

At 1 year, 2 patients in the study group underwent nephroureterectomy, compared to 3 patients in the control group (statistically insignificant difference, $p=0.16$).

At 3 years, the relapse rate was 11.5% in the study group versus 18% in the control group, ($p<0.05$): 7.1% in patients with low-grade lesions and 40% in patients with high-grade lesions versus 21.4% in patients with low-grade lesions and 100% in patients with high-grade lesions (both arms with statistically significant differences, $p<0.05$.

At 3 years, 4 patients in the study group required nephroureterectomy compared to 6 patients in the control group.

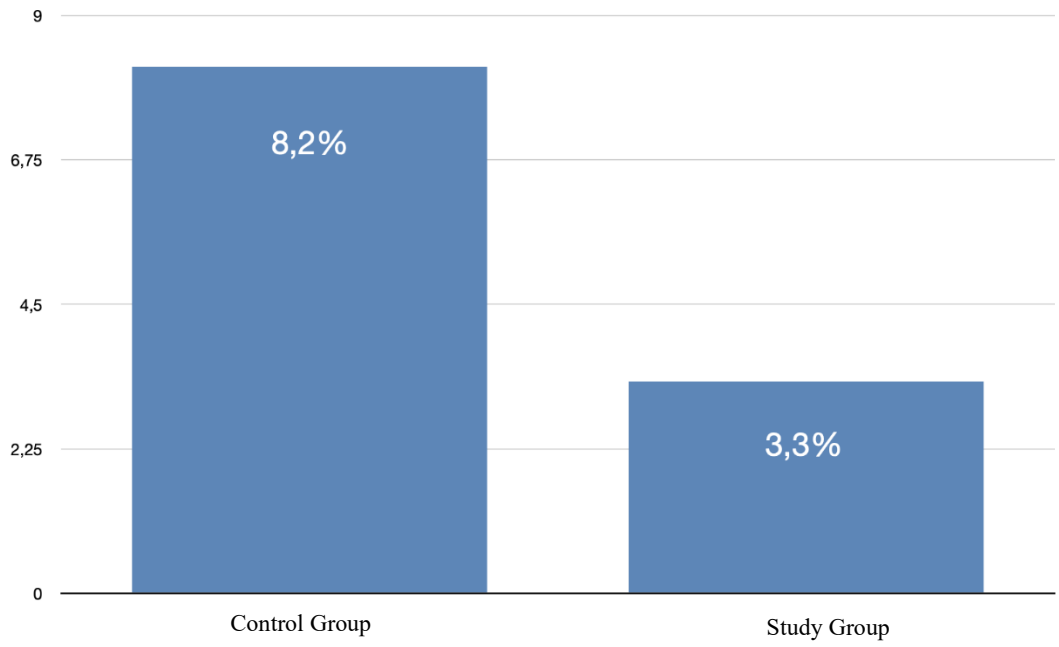

Figure 6.6 Recidivism rate at 3 years (global)

Cancer-specific survival was 93.4% in the study group versus 86.9% in the control group ($p<0.05$).

7. Conclusions

The current study is a pioneer in this field in Romania, and the results obtained are comparable to the few current data available in the specialized literature.

The objectives of the study are to show that flexible ureteroscopy in NBI is superior as a visualization technique than the classic visualization options for intrarenal urothelial carcinoma lesions.

The detection rate of patients with neoplasia was clearly higher in NBI.

The association of NBI was clearly superior in the detection of new cases with UUT-TCC and of additional lesions compared to the standard WL method.

From the point of view of patient follow-up, at 10 weeks, the remaining tumor tissue was statistically significantly smaller in the group of patients in which laser ablation was performed in NBI.

The recurrence rate at 3 years was statistically lower in patients with low-grade tumors whose detection and vaporization was performed in NBI and with a clearly increased statistical significance in those with high-grade tumors whose detection and vaporization was performed only in WL.

Cancer-specific survival at 3 years was statistically higher in the group of patients in whom tumor detection and ablation was performed by NBI technology

Further studies are needed to clarify the impact of this technology on diagnosis, recurrence rate, tumor-free survival, and overall outcome of those patients. Future directions include combining NBI with molecular markers in those at increased risk of UUT-TCC.

In the field of urothelial carcinoma affecting the upper urinary tract, findings in the specialized literature have addressed the issue of false positive results related to NBI-guided biopsies, however, the diagnosis of non-invasive bladder cancer based on endoscopic detection by the NBI visualization technique has been documented and confirmed with a substantially increased frequency unconfirmed malignant lesions until a parallel is made with classical WL endoscopy. Favorable results clearly appear to exist in the category of patients among whom noninvasive urothelial malignancies are detected with imaging technology.

In conclusion, the current data of the preliminary studies carried out so far and carried out with the aim of detecting the sensitivity and sensitivity rates of the NBI technique in the

detection of UUT-TCC in the specialized literature are promising, with results at least comparable to those of the present study.

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