Doctoral School in Medical Sciences

Whit manuscript title
CZU: 616.62-006-072.1-089(043.2)

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DIAGNOSIS AND ENDOUROLOGICAL TREATMENT OF NON-MUSCLE-INVASIVE BLADDER TUMORS

321.22 – UROLOGY AND ANDROLOGY

Summary of Ph.D. Thesis in Medical Sciences

Chișinău • 2024

The thesis was developed at the Department of Urology and Surgical Nephrology, „Nicolae Testemițanu" State University of Medicine and Pharmacy from the Republic of Moldova, and at the Urology Department from „Timofei Moșneaga" IMSP Republican Clinical Hospital.

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The PhD thesis defense will take place on 20.11.2024, at 14:00 on the premises of „Nicolae Testemițanu" State University of Medicine and Pharmacy from the Republic of Moldova, Ștefan cel Mare si Sfănt Ave. 165, office 205, at the meeting of the Commission for Public Defense of PhD thesis, approved by the decision of the Scientific Council of the Consortium of 26.06.2024 *(minutes no.47).*

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CONTENTS

LIST OF ABBREVIATIONS

CI – confident interval
CIS – carcinoma in situ
CUETO – Spanish Urological Oncology Group
BC – bladder cancer
DF – degree of freedom
EAU – European Association of Urology
En-bloc – En-bloc resection
PMSI – Public Medical-Sanitary Institution
IMC – body Mass Index
MIBC – muscle-invasive bladder cancer
NMIBC – non-muscle-invasive bladder cancer
NBI – narrow band imaging
BP – bladder perforation
NMR – nuclear magnetic resonance
ONR – obturator nerve reflex
reTUR – repeat transurethral resection
ECOG – Performance Status Scale
TNM – tumor diagnosis classification according to the TNM system (abbr: **t**umor, **n**odus și **m**etastasis)
TUR – transurethral resection
TUR-V – transurethral resection of bladder
CT – computed tomography
USG – ultrasonogfrafie
WL – white light cystoscopy

THE CONCEPTUAL CHARACTERISTICS OF THE RESEARCH

The relevance and importance of the researched issue.

The diagnosis and treatment of tumors of the urogenital system remain among the current topics of modern urology. Technical-scientific progress in diagnosis, the presence of multiple risk factors, the increase in life expectancy, and the impact of harmful agents have increased the frequency of identification of tumors located in the urinary bladder. Bladder cancer is a serious, disabling disease that tends to recur and progress. Therefore, once identified, the disease requires a differentiated, deep diagnosis and an effective treatment [1, 2].

Among all types of tumors, bladder cancer ranks 4th in the US and 5th in Europe, representing 5.5% of all malignant neoplasms [3, 4]. Among urological tumors, bladder cancer follows in frequency immediately after prostate cancer. In the Republic of Moldova, the morbidity due to bladder cancer has almost doubled from 2000 to the present [5, 6]. Although there is a wide range of diagnostic methods for bladder cancer, the identification of this type of tumor in its early stages and the control of the radical treatment carried out remain always current. Every fifth patient diagnosed with bladder cancer dies from the given pathology within five years of the initial diagnosis. Early diagnosis and treatment offer the possibility of survival beyond 5 years with a rate of approximately 90% [7]. Despite the progress of modern medicine and the possibilities of identification, there is an increase in the incidence of bladder cancer and the number of patients who come in late stages.

The main method of diagnosing bladder tumors is cystoscopy, which allows examination of the appearance of the bladder mucosa with the specification of the number, size, and location of tumor formations. The technique also allows taking a biopsy for morphopathological analysis [8, 9]. There are several methods of cystoscopy: white light cystoscopy, fluorescence cystoscopy, and recently narrow band imaging cystoscopy (NBI) has been proposed as an alternative. Narrow band imaging cystoscopy is a technique that improves the visualization of the mucosal pattern, as well as mucosal and submucosal vessels by using the characteristics of the light spectrum, introduced in clinical practice to more effectively detect bladder tumors. NBI is a technology that, by spectrally visualizing the vascular tissue structure, allows the mapping of blood vessels and other tissue structures on the mucosal surface without the need for a photosensitizer. Thus it becomes possible to highlight the contrast between capillaries and other mucosal structures [10, 11, 12, 13]. The emergence of new diagnostic procedures and the improvement of classical research techniques have greatly facilitated the early detection of bladder tumors and the accurate establishment of the stages of the pathology. Diagnostic and treatment algorithms are constantly subject to adjustment in line with new scientific and technological achievements.

Transurethral resection of bladder formations currently represents the basic therapeutic modality for the treatment of non-muscle-invasive (superficial) bladder tumors. In the case of non-muscle-invasive tumors (Tis, Ta, T1) of the urinary bladder, transurethral resection is performed with a curative purpose and consists of the complete removal of the tumor within the limits of healthy tissue. Resection can be performed by different methods [9, 14, 15, 16]. In recent years, much more attention has been paid to the En-bloc resection method, which allows the complete removal of the tumor within the limits of the healthy tissue and to obtain a more qualitative histopathological evaluation during the morphological examination. En-bloc resection ensures the presence in most cases of the muscle layer in the morphological piece. It also shows more favorable postoperative results [17, 18, 19, 20, 21].

The histopathological examination of the excised tumor tissue is essential in establishing the correct diagnosis and choosing the right method of treatment. Accurate staging allows the initiation of appropriate bladder cancer therapy, which is completely different for non-muscle-invasive and muscle-invasive tumors [22, 23, 24].

The presence of the detrusor muscle layer in the biopsy specimen is one of the quality indicators of endoscopic transurethral resection. The correctness of the histopathological examination depends on the quality of the performed resection, which subsequently becomes valuable for the estimation of the risk group, the detection of recurrence, and the assessment of long-term treatment results [25, 26, 27, 28]. If the muscle layer is absent during the histopathological examination, there is an increased risk of recurrence, residual tumors, and the possibility of underestimating the stage of the disease [25, 29, 30].

The purpose of the research:

Clinico-morphological evaluation of the treatment of non-muscle-invasive bladder tumors for the optimization of endourological diagnostic and treatment methods.

To achieve the purpose of the research, we set the following tasks:

1. Study of clinical and paraclinical aspects of non-muscle-invasive bladder tumors.
2. Comparative evaluation of methods of early diagnosis of non-muscle-invasive bladder tumors by narrow band imaging cystoscopy and white light cystoscopy.
3. Comparative analysis of the quality of the histopathological results according to the applied surgical technique.
4. Comparative research of the results of treatment of non-muscle-invasive bladder tumors by transurethral resection (TUR-V) and En-bloc resection.
5. Development of the algorithm for prognosis of recurrences in patients with non-muscle-invasive bladder tumors.

Scientific research methodology:

A complex study was carried out with the analysis of clinical and paraclinical data of patients with non-muscle-invasive bladder tumors (analysis of contemporary data from specialized bibliographical sources was one of the preliminary stages of the original research). The patients were divided into two research groups according to the applied treatment method. The research included the general evaluation of the patient's status (gender; age; harmful habits - smoking, alcoholism, etc.), the specific urological evaluation (obstructive, irritative syndrome; hematuria, etc.), and the assessment of laboratory indices (clinical analysis of blood and urine), using imaging methods (ultrasonography of the urogenital apparatus), narrow band imaging (NBI) cystoscopy, endourological treatment (TUR-V, En-bloc resection), histopathological analysis—all in a comparative study. The accumulated informative material was analyzed using advanced statistical processing methods.

Scientific novelty and originality:

The paper represents a complex study carried out at the Chair of Urology and Surgical Nephrology of the Nicolae Testemitanu State University of Medicine and Pharmacy and in the Urology Clinic of the PMSI (Public Medical-Sanitary Institution) Republican Clinical Hospital

„Timofei Mosneaga", in which the results of endourological diagnosis and treatment of non-muscle-invasive bladder tumors were comprehensively reviewed.

Based on the accumulated clinical material, a multilateral comparative analysis was performed on the results of early diagnosis, and the effectiveness of various endoscopic treatment methods (En-bloc resection and TUR-V) applied to patients with non-muscle-invasive bladder tumors was estimated.

The value and superiority of using the new method of endourological diagnosis of bladder tumors were demonstrated. Was determined the correlation between the number of tumors detected and the method of cystoscopy used (white light cystoscopy versus narrow band imaging cystoscopy).

The methodology for performing the En-bloc resection method was argued, and the effectiveness of these interventions in patients with non-muscle-invasive bladder tumors was demonstrated. Also, the correlation between the transurethral resection method applied and the number of recurrent tumors was established.

A complex analysis of the morphopathological results was carried out, indicating the importance of the presence in the histological piece of the detrusor muscle layer for the precise establishment of the diagnosis.

Scientific problem solved:

The use of narrow band imaging cystoscopy (NBI), compared with white light (WL) cystoscopy, has been shown to allow the determination of more tumor lesions and increase the early detection of primary tumors and tumor recurrences. Based on the comparative analysis of the treatment methods (En-bloc resection and TUR-V), several advantages of the En-bloc resection intervention were deduced, especially concerning the quality of the histopathological material collected and the rate of postoperative relapses. Factors with prognostic value for assessing the probability of postoperative recurrences were identified.

The theoretical significance and the applied value of the work:

The value of complex clinical and paraclinical evaluation of patients with non-muscle-invasive bladder tumors to predict recurrence and disease progression was demonstrated. The implementation in clinical practice of new transurethral endoscopic methods of diagnosis with the use of NBI allowed the early detection of primary and recurrent tumors.

The implementation and use of transurethral endoscopic intervention of En-bloc resection in the treatment of this urological pathology improved the postoperative results with a reduction of the recurrence rate, especially in the initial resection area.

It has been shown that the accuracy of the established diagnosis depends on the presence of the detrusor (muscle layer) in the material for histopathological examination, which serves as a marker of the quality of the performed resection.

Prognostic factors were identified that argued for the development of a predictive model for determining the probability of recurrence in patients with non-muscle-invasive bladder tumors, depending on the location of the tumor process and the surgical method of treatment applied.

Implementation of scientific results:

The results of the obtained scientific research were applied in the teaching process at the Department of Urology and Surgical Nephrology of the "Nicolae Testemițanu" State University of Medicine and Pharmacy, in the post-graduate training process of urology resident doctors and doctors in the continuous medical improvement courses, in the clinical activity of the urology and

endourology section of Republican Clinical Hospital "Timofei Moșneaga" and in the urology sections of municipal and district hospitals in the Republic of Moldova.

Approval of scientific results:

The materials and results were presented in national and international scientific forums, including:

- The annual scientific conference of SUMP "Nicolae Testemițanu". " Research in Biomedicine and Health: Quality, Excellence, and Performance ". Chisinau, October 19-21, 2022.
- ESU-ESOU Masterclass on Non-Muscle-Invazive Bladder Cancer, 04-05 February 2021.
- Urological Forum: ”Полесский урологический форум” (”Poleskii urologiceski forum”). Gomel State Medical University. 2021 (Belarusians, 2021).
- The annual scientific conference of SUMP "Nicolae Testemițanu". " Research in Biomedicine and Health: Quality, Excellence, and Performance ". Chisinau, October 20-22, 2021.
- Congress Dedicated to the 75th Anniversary of the founding of USMF "Nicolae Testemițanu". Chisinau, October 21 – 23, 2020.
- International Congress for Students and Young Doctors 8th edition of MedEspera, held on May 24 – 26, 2020, Chișinău, Republic of Moldova.
- The 7th Urology, Dialysis, and Renal Transplantation Congress from the Republic of Moldova, with international participation. Chisinau, June 19-21, 2019.
- Conference: Jubilee inter-disciplinary scientific-practical conference. City Center of Endoscopic Urology and New Technologies. Saint Petersburg. 2019. (St. Petersburg, 2019).
- XXXV Congress of the Romanian Association of Urology ROMURO 2019, Bucharest, June 5 – 8, 2019.
- EAU Update on Bladder Cancer Meeting 2019, 17-18 May 2019, Turin, Italy.
- International Congress for Students and Young Doctors 7th edition of MedEspera, held on May 3 – 5, 2018, Chisinau, Republic of Moldova.
- The University Days and the Annual Scientific Conference SUMP "Nicolae Testemițanu". Chisinau, October 15 – 19, 2018.
- The University Days and the Annual Scientific Conference dedicated to the 90th anniversary of the birth of the illustrious doctor and scientist - Nicolae Testemițanu, Chisinau, October 18-20, 2017.

The Ph.D. thesis was discussed, approved, and recommended for defense at a joint meeting of the members of the guiding group, scientific advisor, and Chair of Urology and Surgical Nephrology of the Nicolae Testemitanu SUMPh (minute no. 4, dated November 22, 2023) and at the meeting of the Scientific Seminar 321, and General Medicine Specialties: 321.13, Surgery, 321.14, Pediatric Surgery, and 321.22, Urology and Andrology (minutes No. 7 of June 19, 2024).

The main materials of the thesis have been published in 19 scientific works, including 11 articles and 8 theses; 9 national and 10 international publications, 2 with impact factor; 10 documents implementing the results of scientific research; 3 innovator certificates (No. 5758, 5759, and 5972); 1 intellectual property bulletin (OȘ Series No. 7500).

The Ph.D. thesis received a positive conclusion from the Research Ethics Committee within the "Nicolae Testemitanu" State University of Medicine and Pharmacy (minutes No. 11 of 05/11/2019).

Key words: bladder tumors, cystoscopy, narrow band imaging, transurethral resection, En-bloc resection, tumor recurrence, laser, predictive model.

The volume and structure of the thesis:

The thesis is presented on 103 pages and contains: introduction, 5 chapters, including the synthesis of results, conclusions and recommendations, bibliography (151 sources). The thesis material was illustrated with 39 figures, 33 tables and 6 annexes.

PH.D. THESIS CONTENT

The Introduction section addresses the theoretical aspects of the components analyzed within the research, the topicality of the topic, the purpose and objectives of the study, the novelty and scientific originality of the results obtained, the theoretical and applied significance of the work, the approval of the results obtained and the summary of the thesis sections.

1. EARLY DIAGNOSIS AND TREATMENT OF NON-MUSCLE-INVASIVE BLADDER TUMORS

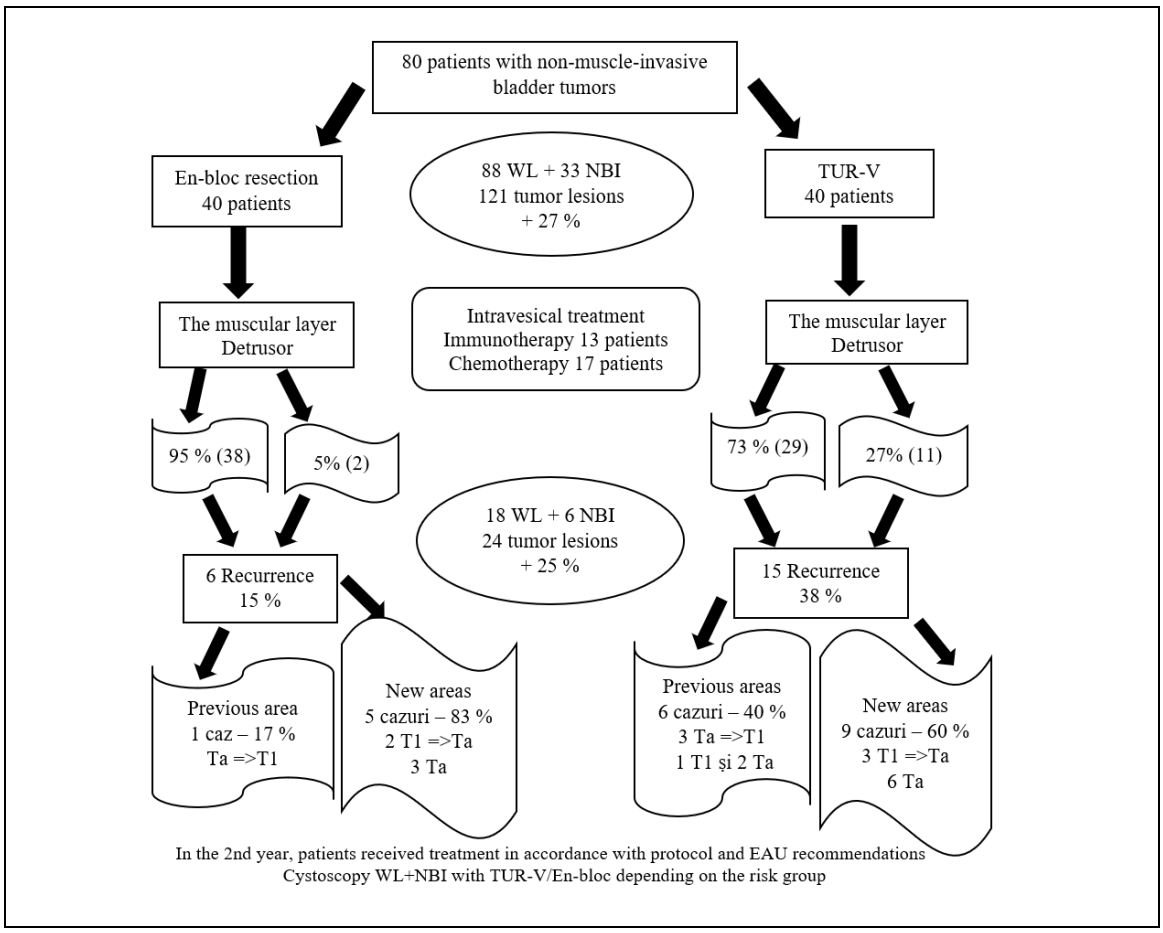
In this chapter, there is a review of the specialized literature regarding the diagnosis and treatment of non-muscle-invasive bladder tumors, analyzing the views presented concerning etiology, risk factors, contemporary diagnostic methods, the use of tumor markers, and the treatment of patients with bladder tumors. According to the literature data in the field, the arguments brought by different authors were analyzed with reference to the usefulness of modern techniques for the early diagnosis of neoplastic pathology in the urinary bladder: white light cystoscopy, fluorescence cystoscopy, and narrow band imaging cystoscopy. In particular, studies evaluating the advantages and limitations of endoscopic treatment methods, including transurethral resection of the urinary bladder and the En-bloc resection method of bladder tumors, were analyzed. The analysis of the specialized literature highlighted the need for comparative deepening and highlighting the effectiveness and harmlessness of endoscopic methods for early diagnosis and endourological treatment of non-muscle-invasive bladder tumors.

2. MATERIAL AND RESEARCH METHODS

2.1 General characteristics of patient groups included in the study

The study is based on the results of the endourological diagnosis and treatment of patients with non-muscle-invasive bladder tumors, who were assisted in inpatient and outpatient conditions in the department of Urology and Endourology of the Republican Clinical Hospital "Timofei Moșneaga", which is the clinical base of the Department of Urology and Surgical Nephrology of the "Nicolae Testemițanu" State University of Medicine and Pharmacy during 2018 - 2022. The respective research is a prospective study. According to the aim and objectives of the work, the patients were divided into 2 research groups to comparatively analyze the diagnostic methods and the results of endourological treatment applied to non-muscle-invasive bladder tumors. In the final study, 80 patients who met all criteria were included for detailed follow-up throughout the study.

Table 1. **Overall study design (years 2018 – 2022; 80 patients)**



The inclusion criteria: men and women over 18 years of age, with clinically and paraclinically (morphologically) confirmed non-muscle-invasive bladder tumors, performance status (ECOG) score 0-2.

The exclusion criteria: developmental abnormalities of the urinary tract, neoplasia of the urinary tract (except the bladder), serious associated diseases or critical health conditions, ECOG score ≥ 3, and pregnancy.

Group I (study group) includes 40 patients with various sizes and shapes of non-muscle-invasive bladder tumors treated by the En-bloc endoscopic resection method.

- The average age of the patients in the base group was 59 years, including 59.25 years for men and 60.1 - for women, the ratio of men to women being 3.4:1.
- Tumors larger than 3 cm were detected in 5 patients, 2 or more tumors were present in 10 out of a total of 40 patients.
- Histopathologically, 24 of the 40 patients had stage Ta tumor, and another 16 patients - had stage T1 tumor; according to the degree of differentiation: G1 was found in 7 patients, G2 - in 20 patients, and G3 - in 13 patients.
- According to location, in 56% of cases, tumors were located on the lateral walls of the urinary bladder, in the trigone of the bladder - in 21% of cases, and in other locations.

Group II (the control group) included 40 patients who underwent transurethral resection of the urinary bladder tumors, constituting the control group for the comparison of the efficiency and harmlessness of the intervention methods. This batch has been completed according to the same selection criteria as in the En-bloc resection batch.

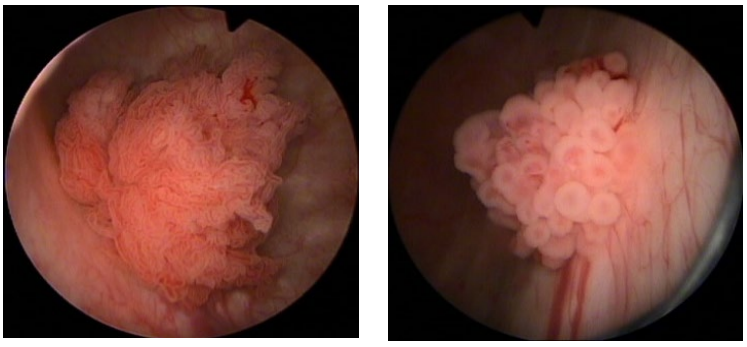
- The average age of patients in the control group was 60 years, including 58.7 years in men and 64.7 years in women, the ratio between men and women being 3.4:1.
- Tumor volume: formations over 3 cm were present in 8 patients, 11 of the 40 patients had 2 or more tumors.
- Histopathologically, in 22 patients, the tumor was assessed in stage Ta, and in 18 patients - stage T1; according to the degree of differentiation, G1 was distinguished in 5 patients, G2 grade was found in 21 patients and G3 grade - in another 14.
- The preferred location of the tumor was also the lateral walls of the urinary bladder - in 70% of cases, followed by the trigone of the bladder - in 14% of cases and other locations.

2.2 The methods and techniques of clinical and paraclinical examination of the patients included in the study.

The investigation of patients with tumoral conditions of the urinary bladder includes the initial stage (preoperative), clinical examination specifying the anamnesis, the characteristics of the evolution of the disease, fixing the patients' accusations, and the clinical manifestations. All patients underwent a complex clinical evaluation: laboratory examination (study of routine parameters and biochemical analysis of blood, summary examination, and bacteriology of urine), imaging, and ultrasonographic research. Risk factors are investigated with particular attention: family history of bladder cancer; harmful habits (smoking); the presence or absence of carcinogenic factors – professional or behavioral, analysis of primary accusations; the reason for presenting the patient for diagnosis and specialized treatment.

2.3 Diagnostic methods and transurethral endoscopic treatment

Cystoscopy is the essential method of diagnosing bladder tumors (Figure 1), being performed on absolutely all patients preoperatively, with the aim of establishing the diagnosis and postoperatively for 12 months, with the aim of evaluating the results of the applied treatment (local tumor recurrences, recurrent tumors, disease progression). Successes in the development of endoscopic diagnostic methods help to obtain high-quality endoscopic imaging and open new directions for early diagnosis during cystoscopy.



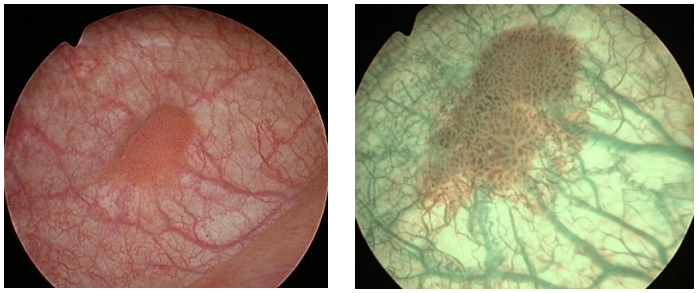
A. Right lateral wall B. Left lateral wall

Figure 1. **Bladder tumors detected during cystoscopy**

Narrow band imaging cystoscopy (NBI) is a new method of endoscopic examination, in which the light source of the endoscopic system has a modified optical filter. White light is filtered in this technique into two light beams, with wavelengths of 425 nm (blue) and 540 nm (green), which are intensely captured by hemoglobin (Figure 2). As a result, the visibility of the capillaries and blood vessels at the level of the submucosa increases. In urothelial carcinoma, which is well vascularized, the contrast between the normal tissue and the tumor tissue is accentuated, thus making it possible to highlight the contrast between the capillaries and other structures of the mucosa and therefore - the effective identification of tumor lesions (especially flat or Cis-type

lesions). NBI allows the modification of the optical spectrum in order to more precisely evaluate the suspicious areas and control the margins of the resections performed.

Surgical treatment of non-muscle-invasive bladder tumors can be performed through several methods, techniques, and procedures. The choice of the surgical procedure and the energy used depends on a series of criteria: the size of the tumor, the underlying pathology, the anesthetic risk, and the equipment available in the clinic. Transurethral bladder resection is currently the gold standard for the treatment of non-muscle-invasive bladder tumors. The goal of the intervention, in the case of non-muscle-invasive bladder tumors, is the correct diagnosis and complete resection of all visible tumors. Endoscopic resection can be performed with the help of electricity (monopolar and bipolar surgery) or with the use of laser energy. Depending on the resection methods, different solutions are used for irrigation: saline - for bipolar or laser resection and distilled water, glycine and sorbitol - for monopolar resection. In order to avoid hypothermia, the irrigation fluid should be at human body temperature..

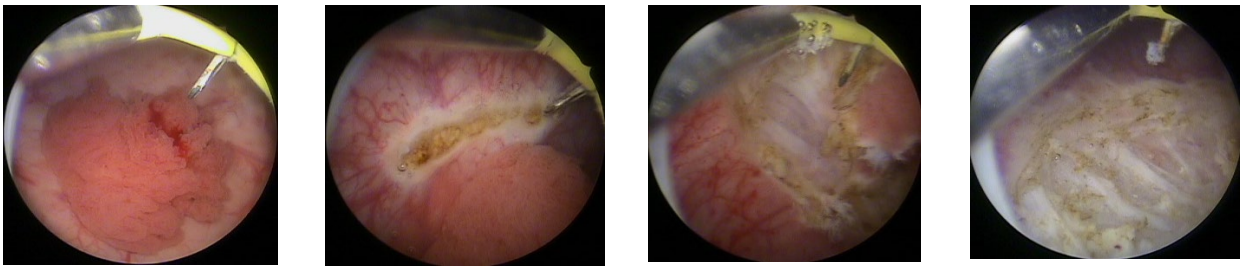


A. White light cystoscopy (WL) B. Narrow band imaging cystoscopy (NBI)

Figure 2. **Endoscopic image of the bladder mucosa**

Conventional transurethral resection of the urinary bladder, during which the exophytic component is removed, subsequently, the tumor leg with the bladder wall up to the muscle layer, the suspicious surfaces are also extracted. Separate sections of the exophytic part of the tumor in the bladder wall and the resection margins provide us with relevant information on vertical and horizontal tumor spread.

The en-bloc resection technique involves circular marking around the tumor, by coagulation, 5-10 mm from the tumor pedicle (Figure 3. A and B). From this level, the incision of the bladder wall is made up of the deep muscles (Figure 3. C and D), and the tumor part is evacuated by aspiration with the syringe. En-bloc resection of bladder tumors offers some advantages: the tumor part presents examination facilities for the anatomopathologist in the absence of coagulation artifacts and fragments, but also the possibility of tumor orientation. En-bloc resection (complete excision of the tumor) is possible for the formation up to 3 cm in diameter and allows for a more accurate morphopathological examination. The presence of detrusor muscle on biopsy specimens after transurethral bladder resection is an indicator of endoscopic resection quality.



A. Tumor visualization B. Marking the resection area C. Tumor resection D. Assessment of the post-resection area

Figure 3. **Endourological picture before and after En-bloc bladder resection (clinical case)**

2.4. Statistical processing of the accumulated informative material

The computerized statistical processing of the obtained data was carried out. The research sample (database) was processed through MS EXCEL and SPSS-26 programs in accordance with statistical laws. In the paper, parametric and non-parametric statistical tests were applied, in order to highlight the significant differences between the values derived from two sampled lots. Descriptive statistics for discrete data included absolute frequency, relative frequency, and 95% confidence intervals, with continuous data described by minimum value, maximum value, mean, median, standard deviation, 25% percentile, and 75% percentile, with data visualized via the bar graph. To test the formulated hypotheses, in particular, to determine the associations between dichotomous variables, the $\chi 2$ test with continuity correction for 2x2 tables was applied, supplemented by OR estimation with 95% confidence intervals. Contingency tables with larger dimensions were analyzed using the classic Pearson $\chi 2$ test. At the same time, for the comparative evaluation between continuous data, the Mann-Whitney U test was applied (a variant for independent batches), the results being visualized through the boxplot graph. The threshold for all tests was $\alpha = 0.05$.

3. STUDY OF CLINICAL MANIFESTATIONS AND EARLY DIAGNOSIS PARAMETERS OF NON-MUSCLE-INVASIVE BLADDER TUMORS

3.1 Analysis of scores and clinical manifestations of non-muscle-invasive bladder tumors

The diagnosis of bladder tumors is made on the basis of clinical investigations, starting with the history of the disease - the onset of the disease, the dynamics of symptoms from the beginning to the moment of addressing the doctor, the application of paraclinical methods - instrumental, laboratory, imaging, etc. Based on the data collected, it was found that the ratio between men and women was 3.4:1 - 62 men (77%) and 18 women (23%) (Table 2).

Table 2**. Distribution of patients with non-muscle-invasive bladder cancer according to gender, hospitalization regime and area of residence (n=80/100%)**

Criterion		Group I		Group II		Total		$\chi 2$ (DF)	P
		abs.	%	abs.	%	abs.	%		
Gender	Men	31	77%	31	77%	62	77%	0,00 (1)	1
	Women	9	23%	9	23%	18	23%		
Total		40	100%	40	100%	80	100%		
Age	18–44 years	5	13%	5	13%	10	13%	0,065 (2)	0,968
	45–59 years	12	30%	11	27%	23	29%		
	60 years and more	23	57%	24	40%	47	58%		
Total		40		40		80	100%		
Area of residence	Urban	17	43%	19	47%	36	45%	0,202 (1)	0,653
	Rural	23	57%	21	53%	44	55%		
Total		40	100%	40	100%	80	100%		
Hospitalization regime	Program regime	37	92%	35	87%	72	90%	0,556 (1)	0,456
	Emergency	3	8%	5	13%	8	10%		
Total		40	100%	40	100%	80	100%		

Note: DF – degree of freedom

The average age is lower for men - 59 years (between 27 and 85 years), the average age for women is 62.4 years (49 - 81 years). Age group breakdown: 12% are from the 18–44 age group, 29% are from the 45–59 age group and 59% are from the over 60 age group. Out of the total number of patients subjected to this study (80 patients), 72 (90%) were admitted to the hospital

under the program regime, under the emergency regime – 8 (10%) patients; $\chi 2 = 0.556$, $P = 0.456$. Emergency admitted patients had recurrent hematuria, refractory to conservative treatment. No significant differences were determined for the conditions and place of living of patients with bladder tumors. Thus, 36 (45%) patients came from the urban environment, and 44 (55%) from the rural environment, $\chi 2 = 0.202$, $P = 0.653$.

The median age of the patients in the investigated groups was 65 years (median, IQR = 20, TUR-V) and 61 years, respectively (median, IQR = 15, En-Bloc), the values being without statistical significance (Mann Whitney test = 759, p = 0.693, two-sided test). From the data presented in Table 2, it follows that the examined groups are homogeneous in terms of gender, age, and treatment method distribution.

Table 3. **Analysis of primary causes (reason for addressing) and estimated risk factors**

Parameters		Group I		Group II		Total		**χ2** (DF)	P
		abs.	%	abs.	%	abs.	%		
Primary complaints	Hematuria	29	73%	30	75%	59	74%	0,128 (2)	0,938
	Dysuria and cystitis clinic	5	12%	4	10%	9	11%		
	Occasional screening	6	15%	6	15%	12	15%		
Total		40	100%	40	100%	80	100%		
Tobacco/ Smoking	Doesn't smoke	25	62%	23	58%	48	60%	0,208 (1)	0,648
	Smokes or has quit smoking	15	38%	17	42%	32	40%		
Total		40	100%	40	100%	80	100%		
Carcinogenic substances	Not reported	36	90%	35	88%	71	89%	0,125 (1)	0,723
	Reported carcinogens	4	10%	5	12%	9	11%		
Total		40	100%	40	100%	80	100%		
Infections, urogenital inflammations in the anamnesis	Present	13	33%	18	45%	31	39%	1,317 (1)	0,251
	Absent	27	67%	22	55%	49	61%		
Total		40	100%	40	100%	80	100%		

Note: USG – ultrasound; DF – degree of freedom

31 (39%) patients requested assistance and were hospitalized for treatment in the first 6 months of the disease, and 49 (61%) - after 6 months, $\chi 2 = 0.053$, $P = 0.818$. Analyzing the primary charges (Table 3), we found that hematuria was revealed in 59 (74%) patients $\chi 2 = 0.128$, $P = 0.938$. Dysuria and clinical cystitis were found in 9 (11%) patients. In 12 (15%) patients the primary tumor was detected during USG, without other obvious clinical manifestations. The number of patients detected occasionally (during routine examinations) is also high. The analysis of risk factors shows the following: smokers (smokers or have smoked in the past) are 32 (40%) patients $\chi 2 = 0.208$, $P = 0.648$; 9 (11%) patients were in contact with carcinogenic substances, $\chi 2 = 0.125$, $P = 0.723$; had infections, urogenital inflammation in history 31 (39%), $\chi 2 = 1.317$, $P = 0.251$.

The evaluation of the patients in the study according to the body mass index - BMI found the following situation: underweight patients (BMI <18.5) - 4 people, patients with normal weight (BMI 18.5-24.9) - 24; overweight (BMI 25.0-29.9) - 29; first-degree obesity (BMI 30.0-34.9) was estimated in 20 people and second-degree obesity (BMI 35.0-39.9) – in another 3. The average

value of BMI was 26.65 (median, IQR = 6.7, TUR-V) and 27 (median, IQR = 5.05, En-Bloc), respectively, with a statistically insignificant difference (Mann Whitney test = 0.808 p = 0.939, two-sided test). There were 23 obese patients (29%), and patients with degree III obesity (BMI ≥ 40) were not certified. Overweight patients are advised to follow a balanced diet (diet); lifestyle changes; and avoid sedentarism.

Patients were also evaluated according to the ECOG score - performance status. Grade 0 was registered in 53 (66%) cases, grade 1 – in 22 (28%) cases, and grade 2 – in 5 (6%) cases. It should be noted that 5 patients with grade 2 ECOG scores are people over 70 years old and have concomitant pathologies (cardiac, gastrointestinal). Non-muscle-invasive bladder tumors are the beginning of a serious, potentially disabling pathology, which calls for the need for an early diagnosis and an effective treatment applied in the early stages to maintain the performance status, which allows the performance of basic daily work and personal self-care.

Anesthesia methods were analyzed and ASA (American Society of Anesthesiology) anesthetic risk was assessed. Among the methods of anesthesia used mainly were total intravenous anesthesia with spontaneous breathing, applied in 52 (65%) cases, and the spinal anesthesia method - in 28 (35%) cases, $\chi 2 = 0.879$, $P = 0.348$. Patients were also assessed according to the ASA anesthetic risk score. Thus, ASA II grade was estimated in 17 (21%) patients, ASA III grade – in 61 (76%) cases, and ASA IV grade – in 2 cases (3%), $\chi 2 = 2.206$, $P = 0.332$. ASA grade IV and, partially, ASA III were appreciated in elderly patients with concomitant diseases. Among the co-morbidities present, cardiovascular pathology predominated, $\chi 2 = 0.069$, $P = 0.793$, and diabetes mellitus, $\chi 2 = 1.127$, $P = 0.288$. A large number of patients with obesity and urinary tract infections were found in all age groups, $\chi 2 = 1.003$, $P = 0.317$.

3.2. Comparative informative value of paraclinical, histopathological and endoscopic diagnostic methods of non-muscle-invasive bladder tumors

Of the total of 80 patients, only 11 (14%) had different clinical changes in the general blood analysis. Anemia was appreciated in 3(4%) cases, leukocytosis with left deviation in the leukocyte formula - in 8(10%) cases. General urine analysis was performed in all patients included in the research. Most patients - 48 (60%) presented with hematuria of different intensity: macrohematuria - in 17 (21%) patients and microhematuria - in 31 (39%), $\chi 2 = 2.277$, $P = 0.320$. Leukocytosis was present in 24 (30%) patients, $\chi 2 = 5.952$, $P = 0.015$. The blood biochemistry results did not reveal significant deviations from the reference parameters.

Bacteriological examination of urine (Uroculture) was performed in all patients, both in the ambulatory regime and during the period of inpatient care. Positive bacteriology was found in 15 (19%) of the patients included in the research. Bacteriuria titer over 105 was found in 8 patients. In parallel, the sensitivity of the detected microorganisms to antibacterial preparations was tested. Microflora analysis showed that in 3 patients Escherichia coli infection predominated and in 1 patient each Proteus, Pseudomonas, Klebsiella, Staphylococcus, and Enterococcus faecalis were found. Patients were given antibacterial treatment according to pre- and postoperative sensitivity.

Figure 4. **Examples of USG and CT of the urinary bladder**

USG examination of the urinary bladder is the first option in the suspicion of tumor pathology of the urinary bladder. USG of the bladder was performed in all patients included in the study, both ambulatory and preoperatively in the hospital. We can note that the method is useful for locating the tumor, and identifying the number and tumor removals, but it has its limits in the case of small formations (of <0.5 cm) and CIS. In 71 (89%) cases, bladder tumors could be visualized by USG examination (figure 4). Computed tomography (CT) and nuclear magnetic resonance (NMR) provide us with conclusive information for selecting the correct method of treatment and, of course, are used in complicated and controversial cases. Investigations were performed on 19 patients (24%) included in the research.

Table 4**. Distribution of patients depending on tumor location**

The location of the tumor	Group I		Group II		Total		$\chi 2$ (DF)	P
	abs.	%	abs.	%	abs.	%		
Dome	1	2%	2	3%	3	2%	3,52 (5)	0,475
Anterior wall	4	7%	2	3%	6	5%		
Posterior wall	8	14%	6	10%	14	12%		
Trigone / bladder neck	12	21%	9	14%	21	17%		
Lateral wall	32	56%	45	70%	77	64%		
Total:	57	100%	64	100%	121	100%		

Note: DF – degree of freedom

As shown in Table 4, a total of 121 formations were identified in the 80 patients, including in Group I - 57 tumors, and Group II - 64. On the lateral walls of the bladder, 77 tumors were detected, in 21 patients the tumor was located in the trigone/neck of the urinary bladder, followed by tumors located on the posterior wall - in 14 cases, but also on the anterior wall - 6 formations, another 3 formations were located on the bladder dome; $\chi 2 = 3.52$, $P = 0.475$. Most patients had solitary tumors, attested in 59 out of 80 patients involved in the study, the rest, 21 patients, had 2 or more tumors, $\chi 2 = 4.441$, $P = 0.488$. In 67 cases the tumors were smaller than 3 cm, and in 13 cases they were ≥3 cm, $\chi 2 = 0.827$, $P = 0.363$.

Analyzing the positioning parameters (Table 4) and the number of identified formations, it can be deduced that solitary tumors (74%) are the top ones, being mainly located on the side walls of the bladder - in 77 (64%) cases, it follows that incidence of tumors located in the Trigon/Neck of the urinary bladder - 21 (17%) cases, formations located on the posterior wall of the urinary bladder was appreciated in 14 (12%) cases. No statistically significant differences were inferred for the indicators of location and number of tumors present. On the other hand, both the site and the number, the tumor sizes become essential at the moment when deciding on the allocation to risk groups, the choice of the surgical method, and the exact treatment formula.

Cystoscopy as an endoscopic (endourological) bladder exploration technique was performed preoperatively in all patients. Initially, white light cystoscopy was performed, after which narrow band imaging cystoscopy (NBI) was used for the early diagnosis of bladder tumors (Figure 5). The method is applied by changing the optical filter in the case of well-vascularized tumors and they stand out much more successfully. During white light cystoscopy in 71 patients, 88 tumors were discovered, additionally, with the help of narrow band imaging cystoscopy, another 33 tumor lesions (+27%) were determined, which were not observed in during white light cystoscopy. In 9 patients, the tumors were detected by the NBI method. The number of tumors detected during NBI cystoscopy, compared to white light (WL) cystoscopy, is statistically significant: Wilcoxon test ($p < 0.001$, two-sided test).

For the definitive diagnosis of a non-muscle-invasive bladder cancer, the morphopathological examination is mandatory. Depending on the stage of the pathology, the type of tumor, and the degree of differentiation, the correct method and next steps of treatment are chosen. The detection of the muscle layer (detrusor) in the histopathological piece is essential for assessing the quality of the performed resection (Table 5 and Figure 6). The accuracy of the histopathological examination also depends on the quality of the performed resection, which, subsequently, becomes valuable for estimating the risk group, revealing recurrence, and assessing long-term treatment results. In cases where the muscle layer is absent during the histopathological examination, there is an increased risk of recurrence, residual tumors, as well as the possibility of underestimating the stage of the disease.

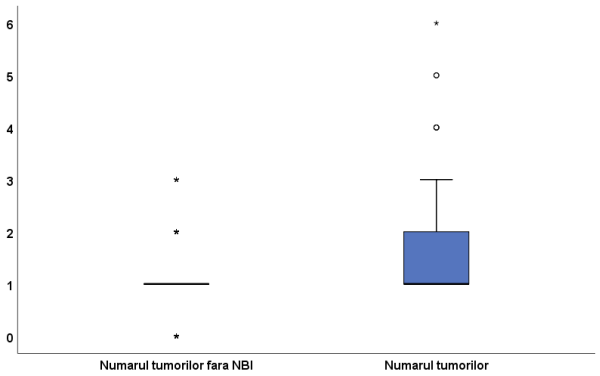


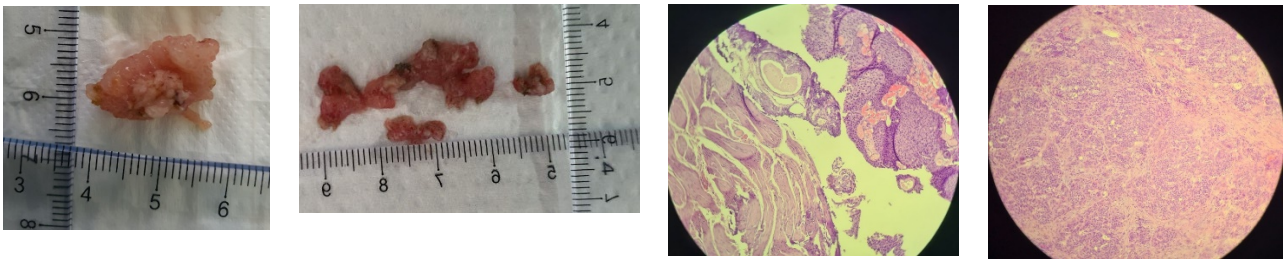
Figure 5. **WL vs NBI crosstab**

Table 5. **Detection of the muscle layer (detrusor) in the piece for histopathological examination**

The presence of the muscle layer		Group I		Group II		Total		$\chi 2$ (DF)	P
		abs.	%	abs.	%	abs.	%		
Detrusor	Present	38	95%	29	73%	67	84%	7,440 (1)	0,006
	Absent	2	5%	11	27%	13	16%		
Total:		40	100 %	40	100 %	80	100 %		

Note: DF – degree of freedom

The detrusor was evident in 38 (95%) of the patients in the group subjected to En bloc resection - the study group and in 29 (73%) of the patients in the control group - with TUR-V intervention, the difference of 22% is also an indicator of statistical significance, $\chi 2 = 7.440$, P = 0.006. In total, 67 (84%) of the patients included in the study had detrusor fragments revealed during the histopathological examination.



Macroscopic En-bloc | Macroscopic TUR-V | Microscopic The presence of the muscle layer | Microscopic Absence of the muscle layer

Figure 6. **The macroscopic and microscopic histopathological picture of the muscle layer (detrusor)**

From the total of 80 patients included in the research, 13 were found to have the absence of the muscle layer (detrusor) in the morphopathological examination piece. In all 13 patients, within 4-6 weeks postoperatively, repeated transurethral resection (reTUR) was performed in order to obtain the muscle layer (biopsy taken from the operative area - biopsy from the scar). Morphological investigations on the samples through the reTUR procedure confirmed the final results in these patients. According to the TNM classification, Ta had 8 patients, T1 – another 5;

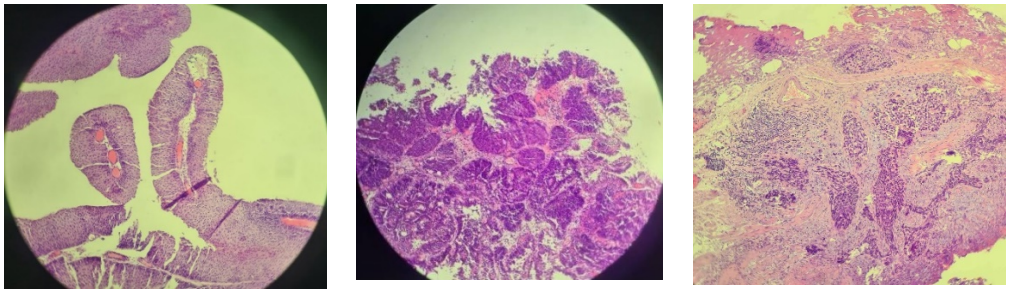
according to the degree of differentiation, G2 was present in 8 patients, G3 - 5 patients, and the presence of detrusor muscle tissue without tumor invasion.

Table 6**. Tumor staging and differentiation**

Parameters		Group I		Group II		Total		$\chi 2$ (DF)	P
		abs.	%	abs.	%	abs.	%		
Tumor staging	Ta	24	60%	22	55%	46	57%	0,205 (1)	0,651
	T1	16	40%	18	45%	34	43%		
Total:		40	100%	40	100%	80	100%		
The degree of differentiation (WHO, 1973)	G1	7	17%	5	13%	12	15%	0,395 (1)	0,821
	G2	20	50%	21	52%	41	51%		
	G3	13	33%	14	35%	27	34%		
Total:		40	100%	40	100%	80	100%		

Note: DF – degree of freedom

Following the analysis of Table 6, we can highlight that in most patients the following were determined: stage Ta in 46 cases and T1 in 34 cases (Figure 7); $\chi 2 = 0.205$, $P = 0.651$. The degree of differentiation according to WHO showed the following results: G1 - 12 cases, G2 - 41 and G3 - 27 cases (Figure 8); $\chi 2 = 0.395$, $P = 0.821$. Patients with G3 differentiation are at increased risk of recurrence and progression and require active oncological evaluation (repeated cystoscopies, intravesical treatment: BCG, mitomycin, doxorubicin).



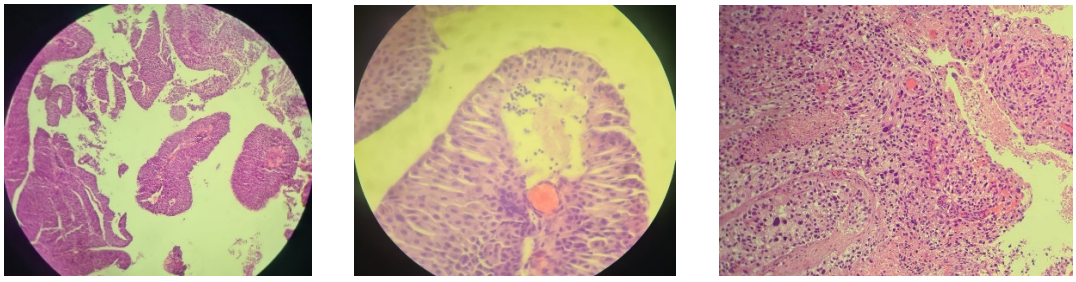
Ta **T1** **T2**

Figure 7**. Microscopic appearance of tumor invasion (TNM)**

Figure 7 shows examples of histopathology investigations depending on the depth of tumor invasion. Bladder cancer is divided into two broad categories, the first refers to non-muscle-invasive cancer – NMIBC, which includes Tis, Ta, and T1. In the case of Ta - non-invasive papillary carcinoma - the microscopic appearance is that of a tumor that does not penetrate the lamina propria, but in the case of T1, the tumor infiltrates the connective subepithelial layer. The second category refers to muscle-invasive cancer - MIBC, which includes T2 - T4. T2 is characterized by tumor infiltration of the muscle layer, subcategory divided into T2a - when the tumor infiltrates the superficial muscle layer (internal half) and T2b - when the tumor infiltrates the deep muscle layer (external half).

One of the most important factors of evolution and occurrence of recurrences in non-muscle invasive bladder cancer, even after adequate treatment, is the degree of histological differentiation of the tumor. Currently, two classifications are used for the histological degree of differentiation: the WHO 1973 grading and the WHO/ISUP 2004 grading. Figure 8 shows examples of morphopathological structuring according to the degree of histopathological differentiation. According to the macroscopic classification, G1 is characterized by clear differentiation of the tumor (papillary urothelial tumor with low malignant potential). G2 is characterized by an average differentiation (papillary urothelial carcinoma with low malignancy) - the cells show moderate

cytonuclear atypia, with loss of polarity, nuclear pleomorphism, and hyperchromasia, predominantly in the basal and intermediate layers. In the worst case - G3 - the tumor is poorly differentiated, and it is difficult to distinguish the component structures of the cells (high-malignancy papillary urothelial carcinoma), histological sections with urothelial epithelium formed by compact atypical cells, marked nuclear pleomorphism, prominent nucleoli, in places aspect of insular growth.



G1 **G2** **G3**

Figure 8. **Microscopic appearance of histopathological grade of differentiation**

Based on the proportions shown in Table 6, the G1 degree of differentiation was appreciated in 12 (15%) patients, 41 (51%) patients present with a G2 degree of differentiation, another 27 (34%) have tumors with G3 degree of differentiation, which also means the highest risk of long-term progression and relapse.

The unfavorable prognostic factors are the following:

- squamous cell carcinoma;
- adenocarcinoma;
- undifferentiated carcinoma;
- low degree of differentiation (G3 according to WHO 1973) or High-grade HG (according to WHO/ISUP 2004);
- tumor size.

4. ANALYSIS OF THE RESULTS OF ENDOUROLOGICAL TREATMENT OF NON-MUSCLE-INVASIVE BLADDER TUMORS APPLIED TO PATIENTS IN THE STUDY

4.1 Complex evaluation of indicators of transurethral endourologic treatment of non-muscle-invasive bladder tumors

In this chapter, the results of endourological treatment applied to non-muscle-invasive bladder tumors are analyzed comparatively (figure 9). A comparative analysis of data obtained following surgical interventions was performed. From group I, 20 patients underwent monopolar en-bloc, 16 bipolar en-bloc, and 4 en-bloc laser, in group II, 22 patients underwent monopolar TUR-V and 18 bipolar TUR-V. Thus, it was determined that the duration of the surgical intervention depends on the location, number, and size of the tumor, but also on the applied surgical method (figure 9). Examination of the data demonstrated that in Group I patients with en-bloc resection, surgery lasted an average of 41 minutes (range, 22 to 57 minutes). In Group II of patients with transurethral resection of the urinary bladder, the average time of the intervention was 43 min (24-55 min). The comparison shows that the operating time of the En-bloc resection is somewhat shorter (by 2 min) than that of the TUR-V intervention; $\chi 2 = 0.231$, $P = 0.891$.

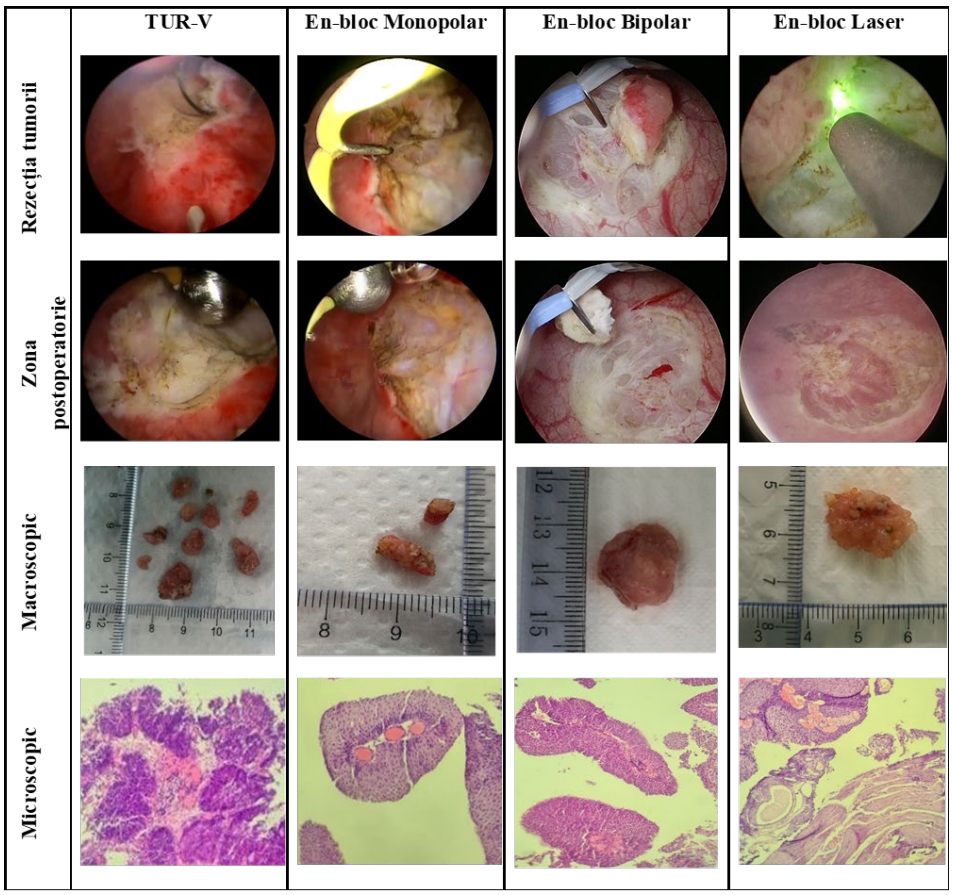


Figure 9. **Intraoperative images with different surgical techniques**

The duration of hematuria depends on the operative method, the number, location, and size of the extracted tumors, the state of the coagulation system, and the presence or absence of concomitant diseases. In Group I the phenomenon of hematuria persisted on average for 1.2 days (1-2 days), in Group II - 1.5 days (between 1 and 5 days); $\chi 2 = 4.211$, $P = 0.240$. Therefore, the duration of postoperative hematuria is not statistically significant. The duration of catheterization of the urinary bladder with a Foley-type urethral probe is on average 2.1 days (between 1 and 5 days) in group I and 2.1 days (1 - 6 days maximum) - in group II of patients with transurethral resection of the urinary bladder. The Foley catheter is preferred in patients with concomitant diseases, considering their age, size, location, and number of excised tumors, as well as intra- and postoperative complications. Duration of bladder catheterization shows no statistically significant difference; $\chi 2 = 1.674$, $P = 0.643$. Bladder irrigation time correlates with the degree of postoperative hematuria.

The hospitalization days/bed index is influenced by several factors: the patient's general condition at admission, associated pathologies, and preoperative preparation (investigations, treatment, recovery of the background pathology). In the En-Bloc group, the mean length of hospital stay was 5 days (range 2 to 10 days). In the TUR-V group, the average duration of hospitalization was also 5 days (variation between 2 and 14 days). No statistically significant differences were observed between the two groups regarding this indicator.

In total, 15 types of complications were determined in the 80 patients included in the research (Table 8). The incidence of postoperative complications is 19%. Most of the recorded complications were grade I (9 complications) and grade II (4 complications). High-grade complications - Clavien-Dindo, grade III, was recorded in 2 cases. During the study period, no cases of death related to transurethral resection of the urinary bladder were recorded.

Among the Clavien-Dindo grade I complications, found in the 2 groups of patients, the following can be noted: transient hematuria, acute urinary retention after postoperative urethral catheter extraction, and urinary tract infection. Hematuria persists for a maximum of 2 days, after which it disappears spontaneously. Acute urinary retention after postoperative Foley urethral catheter extraction is also considered a grade I complication according to Clavien-Dindo, as it can be managed with conservative treatment. This was recorded in 3 patients from group I and 3 from group II. Uncomplicated urinary tract infections were detected in 3 cases, of which: 1 case in the group with en-bloc resection and 2 cases in the group with transurethral resection of the urinary bladder. Intraperitoneal perforations or large extraperitoneal perforations during the bladder resection procedure were not reported. Small extraperitoneal perforations of the urinary bladder (BP) were reported in several patients and were not recorded as complications because the patients were treated without long-term bladder catheterization. Urethral catheters were withdrawn without major deviations from standard practice.

Table 8**. Complications of transurethral resection, classified according to the Clavien-Dindo system**

Parametrii evaluați		Group I		Group II		Total		$\chi 2$ (DF)	P
		abs.	%	abs.	%	abs.	%		
Complications according to the CD Clavien-Dindo classification	Absent	33	83%	32	80%	65	81%	0,126 (3)	0,988
	Grade I	4	10%	5	13%	9	12%		
	Grade II	2	5%	2	5%	4	5%		
	Grade III	1	2%	1	2%	2	2%		
Total		40	100%	40	100%	80	100%		

Note: DF – degree of freedom

Among the grade II Clavien-Dindo complications, recorded in the patients included in the study, should be noted: urinary infections with fever; change in antibacterial treatment, and hematuria, which required blood transfusions. Complicated infections of the urinary tract with fever and the need to change the antibacterial treatment were attested in 4 cases: 2 cases - in the en-bloc resection of the bladder and 2 cases - in the evolution of patients with TUR-V. Persistent hematuria, which required reintervention with endoscopic hemostasis of the bleeding source, was estimated as a grade III Clavien-Dindo complication, the case being from research group II, there was also 1 case from group I with intraoperative damage to the ureteral meatus with anuria postoperative, which required stenting of the ureter. The obturator nerve reflex (ONR) was detected in 11 cases: 5 cases in en-bloc bladder resection and 6 cases during TUR-V. Most often, bladder perforations (BP) are directly related to the obturator nerve reflex, in particular, large extraperitoneal and intraperitoneal perforations. Grade II perforations were recorded in 7 cases: 4 cases in group I and 3 in research group II. General anesthesia, obturator nerve block, and laser energy are used for bladder tumor resections to prevent the obturator reflex and avoid perforations.

4.2. Prognostic indicators, recurrences and development of the pilot predictive model

Among the most important criteria for assessing the success of one or another treatment formula chosen in non-muscle-invasive bladder cancer, the following are distinguished: the time of recurrence, the correct determination of the stage of the disease, and indicators of disease progression. From the overview presented in Table 9, we can see that tumor recurrences were confirmed in 6 patients (15%) after En-bloc resection and in 15 patients (38%) - after TUR-V

intervention, the difference of 23% is one of statistical significance, $\chi 2 = 5.230$, $P = 0.022$. It is also important to mention the site of recurrence, which is of great value for estimating the quality of the performed transurethral resection. We recorded the following results: in group I only 1 out of 6 recurrences was detected in the area of the previous intervention compared to 6 out of 15 recurrences - in group II of the study (the difference is of statistical significance - $\chi 2 = 6.087$, $P = 0.048$. During white light, cystoscopy revealed 18 recurrent tumors, additionally, with the help of narrow-band light cystoscopy, 6 more recurrent tumor lesions were determined (+25%).

Table 9. **Parameters of recurrence produced during the first year post-intervention in the study patients** (80 patients)

The evaluated parameters		Group I		Group II		Total		$\chi 2$ (DF)	P
		abs	%	abs	%	abs	%		
Recurrence	Prezent	6	15%	15	38%	21	26%	5,230 (1)	0,022
	Absent	34	85%	25	62%	59	74%		
Total		40	100 %	40	100 %	80	100 %		
The site of recurrence	Outside the intervention area	5	83%	9	60%	14	67%	6,087 (2)	0,048
	Area of intervention	1	17%	6	40%	7	33%		
Total		6	100 %	15	100 %	21	100 %		

Note: DF – degree of freedom

The time of occurrence of recurrences is a very important moment for the management of patients with bladder tumors. If we analyze the chronology of recurrences (table 9), then we notice that in 8 of the 21 patients, the recurrences occurred in the first 3 months, in 6 patients - after 6 months, in 3 patients - after 9 months, and in 4 patients the recurrences have were highlighted after 12 months postoperatively, $\chi 2 = 5.373$, $P = 0.251$. 67% of recurrences occurred in the first 6 postoperative months (figure 10), which must be taken into account during the dynamic surveillance of patients. Worsening was determined in 4 cases: 2 primary patients with Ta => T1 and 2 patients with G1 => G2. Improvement was observed in 10 cases: in 5 patients with T1 => Ta, in 3 with G3 => G2, and in 2 patients with G2 => G1.

Figure 10. **Cystoscopic image of recurrent tumors**

According to the recommendations of the EAU (European Society of Urology), patients were divided into risk groups which become important when choosing the necessary treatment and differentiating them. Distribution by risk groups: 21(53%) patients in the study group and 23(58%) patients in the control group were in the low-risk group; in the medium-risk group - 9 (22%) patients from the En-bloc resection group and 4 patients (10%) from the TUR-V group; 10 patients (25%) from the study group and 13 patients (32%) from the control group were assessed as high

risk. We found no suggestive data for classification in the very high-risk group. In total, the low-risk group included 44 patients (55%), the medium-risk group – 13 patients (16%), the high-risk group – 23 patients (29%), and 0% - very high risk; $\chi 2 = 2.405$, P = 0.300. Thus, it was found that low-risk patients prevail. Depending on the risk group, the method of treatment and subsequent monitoring of patients is chosen.

The development of the pilot predictive model for determining the probability of recurrence in patients with non-muscle-invasive bladder tumors was based on the localization indicators of the tumor process and the applied treatment method. The development of predictive models involves filling in and/or changing potential covariates from the data validated in the previous chapters.

The null hypothesis is rejected (Omnibus Test of Model Coefficients ($\chi 2 = 18.489$, df = 5, p = 0.002), further analysis shows the following characteristics of the developed alternative model:

The coefficient of determination, Nagelkerke R Square, deduced the value 0.302 (30.2%), which means that compared to the model, one-third of the variance of the variable of interest was explained/covered by the covariates in the modified model. The calibration indicator (Hosmer–Lemeshow test) demonstrated an insignificant value, $\chi 2 = 4.435$, df = 6, p = 0.618, the results being faithful in the sense of anticipating the results obtained over the entire range of predicted scores.

The area under the ROC curve for the predictive model was 0.777, with a 95% confidence interval (0.664 and 0.891) and a significant difference from the value of 0.5 (p = 0.000) (figure 11).

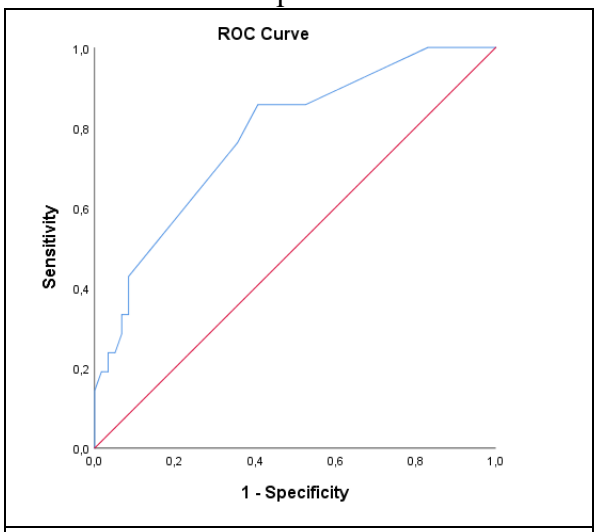


Figure 11. **ROC curve of the prediction model**

Table 10. **Variables in the predictive model equation for the probability of recurrence in patients with non-muscle-invasive bladder tumors**

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper.
Step 1[a]	Intervention	-1,522	,668	5,195	1	,023	,218	,059	,808
	Lateral wall	,892	,408	4,777	1	,029	2,440	1,096	5,431
	Posterior wall	1,468	,767	3,666	1	,056	4,342	,966	19,518
	Anterior wall	1,780	,945	3,548	1	,060	5,931	,930	37,804
	Trigone/bladder neck	-,335	,905	,137	1	,712	,716	,121	4,221
	Dome	-3,755	2,310	2,641	1	,104	,023	,000	2,168
	Constant	-1,601	,638	6,296	1	,012	,202		
Step 2[a]	Intervention	-1,548	,667	5,384	1	,020	,213	,058	,786
	Lateral wall	,947	,383	6,105	1	,013	2,577	1,216	5,460
	Posterior wall	1,558	,735	4,493	1	,034	4,748	1,124	20,047
	Anterior wall	1,869	,923	4,101	1	,043	6,481	1,062	39,560
	Dome	-3,931	2,274	2,989	1	,084	,020	,000	1,691
	Constant	-1,722	,549	9,837	1	,002	,179		

Note: Constanta – the value of the equation constant, B - the coefficients B, S.E.- standard errors, Wald – statistics Wald, df – degree of freedom, Sig.- statistical significance, Exp (B) - odds ratio values (OR), 95%C.I.for EXP(B) - confidence interval for odds ratio

The model included: constant (B = -1.601), procedure value (B = -1.522), lateral wall (B = 0.892), posterior wall (B = 1.468), anterior wall (B = 1.780), trigone/bladder neck (B = -0.335) and bladder dome (B = -3.755), having the appropriate, logical signs in front of the coefficients (Table 10, step 1a). The stability analysis by resampling the alternative model developed for the probability of relapses, the bootstrapping method (1000 samples) demonstrated that the coefficients are stable, the supporting argument being the significance of the parameters, the small amplitude of the confidence intervals and keeping the signs in front of the coefficients in the equation (Table 10, step 2[a]).

Taking into account the mentioned coefficients, the elaborated model has the following mathematical expression:

$$P = \frac{1}{1+e^{-(-1,722+(-1,548)*\text{Intervention}+(0,947)*\text{lateral wall}+(1,558)*\text{Posterior wall}+((1,869)*\text{Anterior wall}+(-3,931)*\text{Dome}}} \quad \text{(Formula 1),}$$

where p – signifies the probability of relapse, e (exponent) – the constant equal to 2,71828

For example, a patient with a tumor formation on the side wall, which was operated by the En-bloc resection method:

$$P = \frac{1}{1+2,71^{-(-1,722+(-1,548)*1+(0,947)*1+(1,558)*0+((1,869)*0+(-3,931)*0}}$$

The risk of recurrence in this patient is 9% (1/11,1 = 0,09)

Components of the modified Step 2 score indicated the following effects: the procedure revealed a positive association with the likelihood of an almost 5-fold reduction in the risk of recurrence (OR = 0.213 (95% CI 0.058, 0.786)) for each tumor in this region. In the case of the lateral wall, the risk of recurrence increases 2.5 times - OR = 2.577 (95% CI 1.216, 5.460) for each tumor with such location. Positioning the tumor on the posterior wall increases the risk 4.7 times - OR = 4.748 (95% CI 1.124, 20.047), and on the anterior wall - by 6.5 times: OR = 6.481 (95% CI 1.062, 39.560). The location of the process on the bladder dome is (OR = 0.02 (95% CI 0.00, 1.691)) for each tumor of the given region. Considering that the pilot predictive model was developed on a relatively small cohort of respondents, our experience can be completed and tested on a larger group of respondents, subsequently being validated for internal and external use.

The discrimination indicators in the classification table, namely, specificity and sensitivity, were equal to 64.4% and 76.2%, respectively, with the summary (global) percentage being valued at 67.5%. The results of these characteristics were reported to the critical point of 0.5.

5. COMPARATIVE SYNTHESIS OF ENDOUROLOGICAL DIAGNOSTIC AND TREATMENT METHODS OF NON-MUSCLE-INVASIVE BLADDER TUMORS

The aim of the present study is to develop the scientific basis to determine early diagnosis methods and differentiated endourological treatment in patients with non-muscle-invasive bladder tumors. Medicine is faced with the aging of the population, with the offensive of risk factors, with the impact of more and more harmful agents, but it is increasingly taking advantage of the fascinating technical and scientific advances that have contributed essentially to the detection of early bladder tumors. Bladder cancer has significant tendencies toward recurrence and progression, for this reason, a rapid diagnosis and radical treatment are needed. BC is a medical problem with important social and economic implications for all states, both economically advanced and those with modest or underdeveloped economies. In most cases, patients present with non-muscle-invasive tumors, which defines a much lower mortality rate compared to bladder cancer that has infiltrated the bladder muscle.

White light cystoscopy is accepted as a standard procedure. The disadvantage of white light cystoscopy is that about 10-20% of actually present bladder tumors are not visualized, especially Cis-type tumor lesions. New imaging techniques may improve the cancer recognition rate compared to WL. Various optical imaging techniques have been devised as adjuncts to WL to increase the visibility of tumors by enhancing contrast. In order to validate a new visualization technique during cystoscopy, it is necessary that it comply with at least two goals: 1 - to increase the accuracy of diagnosis in the detection of bladder cancer and 2 - for the transurethral treatment technique to decrease the risk of progression and/or recurrence. Narrow band imaging cystoscopy (NBI) was introduced into practical use to improve the therapeutic and diagnostic approach to non-muscle-invasive bladder tumors. Narrow band imaging cystoscopy provides more favorable results for the early diagnosis of non-muscle-invasive tumors compared to white light cystoscopy. It requires only the right equipment to perform. The technique is easy to apply - by pressing a single button, without using additional medical substances.

Transurethral resection of bladder tumors (TUR-V) was first described by Stern and McCarthy in 1931 and is still considered the gold standard in the diagnosis and treatment of NMIBC. The quality of TUR-V interferes with the accuracy of histopathological assessment and subsequently with the risk of recurrence and curative outcome. That is why new and new attempts are being made to improve the effectiveness of transurethral resection, and more efficient techniques of interventions and image improvement are also proposed. The objective of transurethral resection is to obtain an adequate tissue specimen for determining the stage and grade of the tumor (diagnostic), and then to resect all visible lesions (therapeutic). Complete resection, including the sampling of the underlying muscularis propria, is recommended by European Urological Association (EAU) and American Urological Association (AUA) guidelines.

En-bloc resection is a promising new surgical technique that involves circular incision of the mucosa at a safe distance from the lesion, followed by preparation and removal of the entire tumor, including the underlying detrusor muscle. The En-bloc resection technique of non-muscle-invasive bladder tumors has been shown to be a safe and effective method compared to the conventional transurethral resection (TUR-V) technique. This method provides more favorable results by taking better quality tumor samples (with fragments of detrusor muscle), which allow the correct diagnosis, accurate staging of the process, and a reduced number of recurrences.

GENERAL CONCLUSIONS

1. The study of clinical and paraclinical aspects of non-muscle-invasive bladder tumors is particularly important for the identification and effective management of these conditions. An integrated approach, combining clinical data with information from paraclinical investigations, can help to establish an accurate diagnosis and choose the most appropriate therapeutic strategy for the patient.
2. The basic method for the diagnosis of non-muscle-invasive bladder tumors remains cystoscopy. The obtained data indicate that using the narrow band imaging (NBI) cystoscopy method increases the quality of visualization of non-muscle-invasive bladder tumors manifested by the detection rate of primary tumor lesions and recurrences. NBI cystoscopy offers the chance of early detection of tumors at statistically significant rates: Wilcoxon test ($p < 0.001$).
3. The evaluation of the histological results demonstrates that through the En-bloc method of resection, we obtain more often the sampling of the muscle layer of the detrusor compared to TUR-V (95% - En-bloc vs 73% TUR-V, $p = 0.006$), which means better quality material for histopathologic examination and correct diagnosis.
4. The comparative analysis of the methods of surgical treatment through transurethral resection (TUR-V) and technique of En-bloc resection of bladder tumors determined that the incidence of intra- and postoperative complications of these techniques are almost equal (without statistically significant differences), only that En-bloc resection reduces the rate of postoperative recurrences (15% - En-bloc vs 38% - TUR-V, $p = 0.022$), especially in the initial resection area (En-bloc - 17% vs TUR-V - 40%, $p = 0.048$) by 23%.
5. The developed predictive model allows estimating the probability of recurrence in patients with non-muscle-invasive bladder tumors, depending on the location of the tumor process and the surgical treatment method applied.

PRACTICAL RECOMMENDATIONS

1. The use of narrow band imaging (NBI) cystoscopy improves the quality of visualization of tumor formations and thus can facilitate the earlier identification of tumors.
2. To reduce the rate of postoperative recurrences, it is recommended to use the En-bloc resection method, which shows more favorable results compared to the classic transurethral resection.
3. To establish a precise diagnosis and choose the appropriate treatment, it is recommended to perform endoscopic intervention with the sampling of the muscle layer of the bladder (detrusor).
4. For the wider application area and the minimum rate of intra- and postoperative complications, the use of bipolar electrosurgery and laser energy is indicated, including for the sampling of more histologically informative fragments.
5. The regimen of therapy after transurethral resection of the urinary bladder must be developed according to the risk group of the respective patient.
6. To estimate the probability of recurrence of bladder tumors, it is recommended to use the predictive model, which considers the location of the tumor process and the surgical method of treatment.
7. During the period of postoperative surveillance, cystoscopy is mandatory, because it allows the early determination of tumor recurrences in the useful therapeutic phase.
8. Computed tomography with the urographic phase is recommended in cases of selective localization of bladder tumors (trigonal tumors, multiple or high-risk tumors).

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- **Implementation acts:**

30. 10 Implementation Acts: 2 in the scientific-didactic activity and 8 in the scientific-practical activity.

ADNOTARE

Vladanov Ivan

„Diagnosticul și tratamentul endourologic al tumorilor vezicale non-muscular invazive”

Teză de doctor în științe medicale, Chișinău, 2024

Structura tezei: lucrarea este prezentată pe 103 pagini și include: introducere, 5 capitole inclusiv sinteza rezultatelor, concluzii și recomandări, bibliografia, care citează 151 de surse, 33 tabele, 39 figuri, 6 anexe. Rezultatele obținute au fost relatate în 19 publicații științifice, inclusiv 2 cu impact factor. **Cuvinte-cheie:** tumorile vezicii urinare, NMIBC, cistoscopie, WL, lumină în bandă îngustă, NBI, rezecția transuretrală, TUR-V, En-bloc rezecția, recurența tumorală, laser, model predictiv. **Domeniul de studiu:** 321.22 – Urologie și andrologie. **Scopul:** evaluarea clinico-morfologică a tratamentului tumorilor non-muscular invazive ale vezicii urinare pentru optimizarea metodelor de diagnostic și tratament endourologic. **Obiectivele cercetării:** studierea aspectelor clinice și paraclinice a NMIBC; evaluarea comparativă a metodelor de diagnostic precoce al NMIBC prin cistoscopia cu lumină în bandă îngustă (NBI) și cistoscopia cu lumină albă (WL); analiza comparativă a calității rezultatelor histopatologice în funcție de tehnica chirurgicală aplicată; cercetarea comparativă a rezultatelor de tratament al NMIBC prin rezecție transuretrală (TUR-V) și En-bloc rezecție; elaborarea algoritmului de pronostic a recidivelor la pacienții cu NMIBC. **Noutatea și originalitatea științifică**: în baza materialului clinic acumulat s-a efectuat o analiză multilaterală comparativă asupra rezultatelor de diagnostic precoce și s-a estimat eficacitatea diverselor metode de tratament endoscopic (En-bloc rezecție și TUR-V) aplicate pacienților cu NMIBC; a fost demonstrată valoarea și superioritatea utilizării metodelor noi de diagnostic endourologic al NMIBC. A fost determinată corelația între numărul tumorilor depistate și metoda de cistoscopie utilizată (WL vs NBI); a fost argumentată metodologia de executare a metodei de En-bloc rezecție și demonstrată eficiența acestor intervenții la pacienții cu NMIBC; s-a efectuat analiza complexă a rezultatelor morfopatologice, din care rezultă importanța prezenței în piesa histologică a stratului muscular detrusor pentru stabilirea precisă a diagnosticului. De asemenea, s-a stabilit corelația dintre metoda de rezecție transuretrală aplicată și numărul de tumori recurente. **Problema științifică soluționată în studiu:** a fost demonstrat că utilizarea cistoscopiei NBI, în comparație cu cistoscopie WL, permite determinarea mai multor leziuni tumorale și sporește detectarea precoce a tumorilor primare și a recidivelor tumorale. În baza analizei comparative a metodelor de tratament (En-bloc rezecție și TUR-V) a fost deduse o serie de avantaje ale intervenției de En-bloc rezecție, în special cu referire la calitatea materialului histopatologic recoltat și la rata de recidive postoperatorii. Au fost identificați factorii cu valoare prognostică pentru aprecierea probabilității recidivelor postoperatorii. **Semnificația teoretică și valoarea aplicativă a lucrării:** a fost demonstrată valoarea evaluării clinice și paraclinice complexe a pacienților cu NMIBC în vederea prognozării recidivelor și progresării maladiei. Implementarea în practica clinică a metodelor endoscopice transuretrale noi de diagnostic cu utilizarea NBI a permis detectarea precoce a tumorilor primare și recidivante. Implementarea și utilizarea intervenției endoscopice transuretrale de En-bloc rezecție în tratamentul acestei patologii urologice a ameliorat rezultatele postoperatorii cu reducerea ratei de recidive, în special în zona de rezecție inițială. S-a demonstrat că precizia diagnosticului depinde de prezența detrusorului (stratului muscular) în materialul pentru examinarea histopatologică, care servește drept marker al calității rezecției efectuate. S-au identificat factori de pronostic ce au argumentat elaborarea modelului predictiv pentru determinarea probabilității recidivei la pacienții cu NMIBC în funcție de localizarea procesului tumoral și metoda chirurgicală de tratament aplicată. **Implementarea rezultatelor științifice:** Rezultatele tezei au fost implementate în procesul didactic și curativ la Catedra de urologie și nefrologie chirurgicală a USMF „Nicolae Testemițanu”, Clinica Urologie, Dializă și Transplant Renal a Spitalului Clinic Republican „Timofei Moșneaga” și alte secții de urologie din Republica Moldova.

АННОТАЦИЯ

Владанов Иван

„Диагностика и эндоурологическое лечение мышечно-неинвазивных опухолей мочевого пузыря”

Диссертация на соискание ученой степени кандидата медицинских наук, Кишинев, 2024

Структура диссертации: Работа представлена на 103 страницах и включает: введение, 5 глав с обобщением результатов, выводы и рекомендации, библиография в которой цитируется 151 источник, 33 таблицы, 39 фигур, 6 приложений. Полученные результаты отражены в 19 научных публикациях, в том числе 2 с импакт-фактором. **Ключевые слова:** опухоли мочевого пузыря, NMIBC, цистоскопия, WL, узкоспектральная визуализация, NBI, трансуретральная резекция, TUR-V, резекция единым блоком, En-bloc, рецидив опухоли, лазер, предиктивная модель. **Область исследования:** 321.22 – Урология и андрология. **Цель:** клинико-морфологическая оценка результатов лечения мышечно-неинвазивных опухолей мочевого пузыря для оптимизации эндоурологических методов диагностики и лечения. **Задачи исследования:** изучение клинических и параклинических аспектов NMIBC; сравнительная оценка методов ранней диагностики NMIBC методами узкополосной цистоскопии (NBI) и цистоскопии в белом свете (WL); сравнительный анализ качества гистопатологических результатов в зависимости от примененной хирургической техники; сравнительное исследование результатов лечения NMIBC методами трансуретральной резекции (TUR-V) и En-bloc резекции; разработка прогностической модели определения вероятности рецидива у больных NMIBC. **Научная новизна и оригинальность:** на основе накопленного клинического материала проведен многосторонний сравнительный анализ результатов ранней диагностики и оценена эффективность различных эндоскопических методов лечения (En-bloc резекция и TUR-V), применяемых у больных NMIBC; Показана ценность и превосходство использования новых методов эндоурологической диагностики NMIBC; определяли корреляцию между количеством обнаруженных опухолей и использованным методом цистоскопии (WL vs NBI); аргументирована методика выполнения метода En-bloc резекции и продемонстрирована эффективность данных вмешательств у больных NMIBC; проведен комплексный анализ морфопатологических результатов, из которого вытекает важность наличия мышечного слоя детрузора в гистологическом препарате для точного установления диагноза. Также установлена корреляция между примененным методом трансуретральной резекции и количеством рецидивов опухолей. **Научная задача, решаемая в процессе исследования:** показано, что применение NBI цистоскопии по сравнению с WL цистоскопией позволяет определить большее количество опухолевых поражений и повышает раннее выявление первичных опухолей и рецидивов опухолей. На основе сравнительного анализа методов лечения (резекция En-bloc и TUR-V) выявлен ряд преимуществ резекционного вмешательства En-bloc, особенно в отношении качества собранного гистопатологического материала и частоты послеоперационных рецидивов. Выявлены факторы, имеющие прогностическое значение для оценки вероятности послеоперационных рецидивовю **Теоретическая и прикладная ценность работы:** продемонстрирована ценность комплексного клинического и параклинического обследования больных NMIBC с целью прогнозирования рецидивов и прогрессирования заболевания. Внедрение в клиническую практику новых трансуретральных эндоскопических методов диагностики с использованием NBI позволило на ранней стадии выявить первичные и рецидивные опухоли. Внедрение и использование трансуретрального эндоскопического вмешательства En-bloc резекции в лечении данной урологической патологии позволило улучшить послеоперационные результаты с уменьшением частоты рецидивов, особенно в зоне начальной резекции. Выявлены прогностические факторы, которые послужили аргументом в пользу разработки прогностической модели определения вероятности рецидива у больных NMIBC в зависимости от локализации опухолевого процесса и примененного хирургического метода лечения. **Внедрение научных результатов:** результаты диссертации внедрены в учебном и лечебном процессах на кафедре урологии и хирургической нефрологии ГУМФ им. Николае Тестемицану, в Клинике урологии, диализа и трансплантации почек Республиканской Клинической Больницы им. Тимофей Мошняги и других урологических отделениях Республики Молдовы.

ANNOTATION

Vladanov Ivan

„Diagnosis and endourological treatment of non-muscle-invasive bladder tumors”

Doctoral thesis in medical sciences, Chisinau, 2024

Thesis structure: the work is presented on 103 pages and includes: introduction, 5 chapters with a synthesis of the results, conclusions and recommendations, bibliography, which cites 151 source, 33 tables, 39 figures, 6 annexes. The results obtained were reported in 19 scientific publications, including 2 with impact factor. **Keywords:** bladder tumors, NMIBC, cystoscopy, WL, narrow band imaging, NBI, transurethral resection, TUR-V, En-bloc resection, tumor recurrence, laser. **Field of study:** 321.22 – Urology and andrology. **Purpose:** clinico-morphological evaluation of the treatment of non-muscle-invasive bladder tumors for the optimization of endourological diagnostic and treatment methods. **Research objectives: s**tudy of clinical and paraclinical aspects of NMIBC; comparative evaluation of the methods of early diagnosis of NMIBC by narrow band imaging (NBI) cystoscopy and white light cystoscopy (WL); comparative analysis of the quality of the histopathological results according to the applied surgical technique; comparative study of the results of treatment of NMIBC by transurethral resection (TUR-V) and En-bloc resection; development of the algorithm for prognosis of recurrences in patients with NMIBC. **Scientific novelty and originality:** based on the accumulated clinical material, a multilateral comparative analysis was performed on the results of early diagnosis, and the effectiveness of various endoscopic treatment methods (En-bloc resection and TUR-V) applied to patients with NMIBC was estimated; the value and superiority of using the new method of endourological diagnosis of NMIBC were demonstrated. Was determined the correlation between the number of tumors detected and the method of cystoscopy used (WL vs NBI); the methodology for performing the En-bloc resection method was argued, and the effectiveness of these interventions in patients with NMIBC was demonstrated; a complex analysis of the morphopathological results was carried out, indicating the importance of the presence in the histological piece of the detrusor muscle layer for the precise establishment of the diagnosis. Also, the correlation between the transurethral resection method applied and the number of recurrent tumors was established. **The scientific problem solved by the study:** the use NBI cystoscopy, compared with WL cystoscopy, has been shown to allow the determination of more tumor lesions and increase the early detection of primary tumors and tumor recurrences. Based on the comparative analysis of the treatment methods (En-bloc resection and TUR-V), several advantages of the En-bloc resection intervention were deduced, especially concerning the quality of the histopathological material collected and the rate of postoperative recurrences. Factors with prognostic value for assessing the probability of postoperative recurrences were identified. **Theoretical significance and application value of the work:** the value of complex clinical and paraclinical evaluation of patients with NMIBC to predict recurrence and disease progression was demonstrated. The implementation in clinical practice of new transurethral endoscopic methods of diagnosis with the use of NBI allowed the early detection of primary and recurrent tumors. The implementation and use of transurethral endoscopic intervention of En-bloc resection in the treatment of this urological pathology improved the postoperative results with a reduction of the recurrence rate, especially in the initial resection area. It has been shown that the accuracy of the established diagnosis depends on the presence of the detrusor (muscle layer) in the material for histopathological examination, which serves as a marker of the quality of the performed resection. Prognostic factors were identified that argued for the development of a predictive model for determining the probability of recurrence in patients with NMIBC, depending on the location of the tumor process and the surgical method of treatment applied. **Implementation of scientific results:** the results of the thesis were implemented in the didactic and curative process at the Department of Urology and Surgical Nephrology, SUMP „Nicolae Testemitanu”, Urology, Dialysis and Renal Transplant Clinic, from the Republican Clinical Hospital „Timofei Mosneaga” and other urology departments of Republic of Moldova.

VLADANOV Ivan

DIAGNOSIS AND ENDOUROLOGICAL TREATMENT OF NON-MUSCLE-INVASIVE BLADDER TUMORS

321.22 – UROLOGY AND ANDROLOGY

Approved for printing: Offset paper. Digital print. Pattern sheets: 2.0	Paper format: A4 Circulation: 25 ex. Order no.:

Typography

Str.

Tel.: