MEDICAL UNIVERSITY - PLEVEN
Faculty of Medicine
Department of Urology

Dr. Nikolay Ivanov Nikolov

A MULTIDISCIPLINARY APPROACH IN THE TREATMENT AND FOLLOW-UP OF PATIENTS WITH NON-MUSCLE INVASIVE BLADDER CARCINOMA

ABSTRACT

of a dissertation for awarding the educational and scientific degree "DOCTOR"

Pleven, 2022

MEDICAL UNIVERSITY - PLEVEN
Faculty of Medicine
Department of Urology

Dr. Nikolay Ivanov Nikolov

A MULTIDISCIPLINARY APPROACH IN THE TREATMENT AND FOLLOW-UP OF PATIENTS WITH NON-MUSCLE INVASIVE BLADDER CARCINOMA

ABSTRACT

of a dissertation for awarding the educational and scientific degree "DOCTOR"

Professional direction: 7.1 "Medicine"

Scientific specialty: "Urology"

Scientific supervisors:

Associate Professor Dr. Boyan Atanasov Stoykov, Ph.D

Associate Professor Dr. Vladislav Rosenov Dunev, Ph.D.

Pleven, 2022

The dissertation consists of 156 pages and is illustrated with 46 figures and 39 tables. The bibliographic list includes 230 literary sources.

The dissertation work has been approved and sent for defense by the extended departmental council of the Department of "Nursing Surgical Care" to the Medical Center of Pleven University of Medical Sciences.

The public defense of the dissertation work will be held on 16.12.2022 from 12 o'clock in the hall “Conference hall“ of “Saint Marina “ hospital.

The defense materials are published on the website of the Medical University-Pleven (http://www.mu-pleven.bg/)

CONTENT

I. Introduction…..…….5

II. Aim and objectives…….…….6

III. Materials and methods...…… 7

1. Survey design…….……..7

2. Object and location of the study……...7

2.1. Criteria for inclusion in the study ……...……....9

2.2. Exclusion criteria in the study ……..……....10

3. Methods of study …….……...10

3.1. Sources of information ……....10

3.2. Statistical methods ……...10

3.3. Diagnostic methods ….……....11

3.3.1. Non-invasive methods of diagnosis ….……....11

3.3.2. Invasive methods of diagnosis …….……....11

3.4. Operative methods of treatment .……12

3.4.1. Monopolar resection ….……...12

3.4.2. Bipolar resection …..……15

3.4.3. Laser resection ….……18

3.5. Conservative methods ...……..20

3.5.1. Intravesical therapy ……..……21

3.5.1.1. Mitomycin ..……...…21

3.5.1.2. Epirubicin ……..22

3.5.1.3. BCG……...…22

3.5.2. Highly focused radiotherapy ……..……..23

3.5.3. Immunotherapy…….24

3.5.4. Nutrition in urothelial carcinoma ……24

3.5.5. Healthy lifestyle …….…….25

IV. Results ….……27

V. Discussion ...……..60

VI. Conclusions...……....75

VII. Applications ...…….77

VIII. References used ……...……..85

IX. Contributions of the thesis ……...85

X . Publications related to the thesis ……...……85

Glossary of abbreviations used:

ALA - aminolevulinic acid

BCG - Bacillus Calmette-Guerinne

DLT - distant radiation therapy

IHC - immunohistochemistry

LDO - laser tumour destruction

RT - radiation therapy

MMS - Mitomycin C

EPI-Epirubicin

NMIBC - nonmuscle invasive bladder cancer

ROD - single focal dose

SOD - total focal dose

mTURB - monopolar transurethral resection

bTURB- bipolar transurethral resection

PDD - Photodynamic Diagnosis

XT - chemotherapy

BUD- Bulgarian Urological Society

BOND - Bulgarian Oncological Scientific Society

AUA- American Urological Association CIS - carcinoma in situ

EAU- European Association of Urology

EORTC - European Organisation for Research and Treatment of Cancer

WHO - World Health Organization

I. Introduction

Bladder carcinoma is a heterogeneous disease in molecular, histological and clinical aspects. In recent years, more and more young people are becoming ill and this requires a new strategy in diagnosis and treatment. Risk factors predisposing to the development of bladder cancer include: patient's age, gender, race, exposure to toxins such as dyes, soot, heavy metals, rubber, plastics, environmental factors (elevated arsenic level in water, chlorine disinfectants and nitrates), lifestyle and dietary factors- smoking, coffee, urinary tract infection. For this reason, its treatment is multidisciplinary: surgery, intravesical and systemic chemotherapy or immunotherapy, radiotherapy, and lifestyle modification.

Bladder carcinoma is one of the most common tumors of the urinary system. The male:female ratio ranges from 6:1 to 2:1. In men it is the 4th cause of cancer and 8th cause of death. Over 90% have the characteristics of transitional cell carcinoma. Prognosis is determined not only by the Ta, T1 and G stages but also by the number of lesions and the recurrence rate with increasing G. The bladder is adjusted well to intravesical administration of chemotherapeutics and radiation therapy. In stage Ta and T1 the 5-year survival after radiotherapy is 60%-80% with 58% in T2 and 38% in T3. After transurethral resection alone, stage T1G3 disease has high recurrence and progression. About 50% of tumors progress to invasive carcinoma.

Transitional cell carcinoma is the most common histology of bladder cancer (~90%) diagnosed in Europe and the US, followed by squamous cell (2-5%), adenocarcinoma (2%), neuroendocrine (1%), and other rare tumors (<1%). The epithelial mucosa of the urinary tract is made up of 5 to 7 cell layers. Tumors that are confined to the bladder and do not invade the muscularis propria are considered nonmuscle-invasive bladder cancer (NMIBC), consisting of stages

Ta, T1, and carcinoma in situ (CIS). Involvement of the muscularis propria is the so-called muscle-invasive bladder cancer (MIBC).

II. Aim and objectives

1. Aim of the study

The aim of this study is to develop a multidisciplinary approach to the treatment and follow-up of patients with superficial urothelial carcinoma of the bladder.

2. Objectives of the study

Objective 1. To develop an algorithm to select patients suitable for transurethral resection.

Objective 2. To investigate the safety of transurethral monopolar, bipolar and laser resection in patients with superficial urothelial carcinoma of the bladder.

Objective 3. To investigate the clinical effectiveness of different methods of transurethral surgery on local tumor control.

Objective 4. To study the pharmacodynamics and pharmacokinetics of various chemotherapeutics and topical immunotherapeutics in patients with superficial urothelial carcinoma of the bladder.

Objective 5. To investigate the impact and side effects of local radiotherapy in patients with superficial bladder cancer.

Objective 6. To investigate the influence of comorbidity, diet and smoking on the occurrence of primary and recurrent superficial bladder cancer.

Objective 7. To develop a multimodal algorithm for the diagnosis, treatment and follow-up of patients with overlying bladder cancer.

III. Materials and methods

1. Survey design

The dissertation is based on a 10-year multicentered prospective study, the study design, informed consent form, diagnostic, surgical, and therapeutic methods

used are consistent with and meet medical standards in urology, medical oncology, and radiology.

Detailed written and verbal explanations in the form of informed consent were given to all the subjects about the treatment methods in the study.

2. Object and place of the study

The study included 444 people - men and women over 18 years of age, Bulgarian citizens, admitted for treatment in the Department of Urology at KOC Vratsa, Clinic of Urology at University Hospital "St. Marina" Pleven, Department of Medical Oncology at KOC Vratsa and Radiotherapy Center at KOC Vratsa in the period from January 2011 to December 2020. 342 men and 102 women participated in the study (Figure 1). For the period 2014-2020, more than 90 % of the examined patients were included (Figure 2).

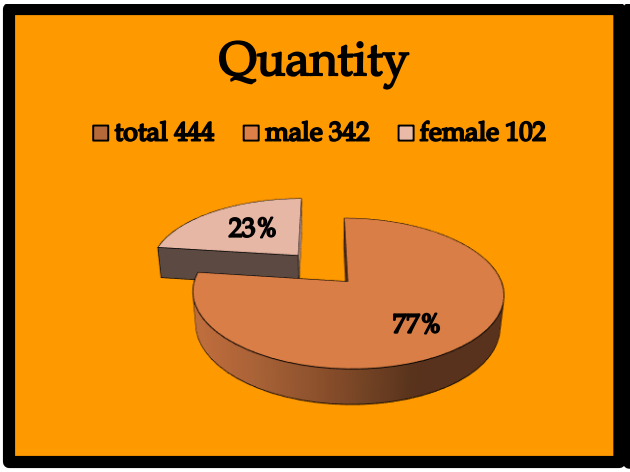


Figure 1. Distribution by sex

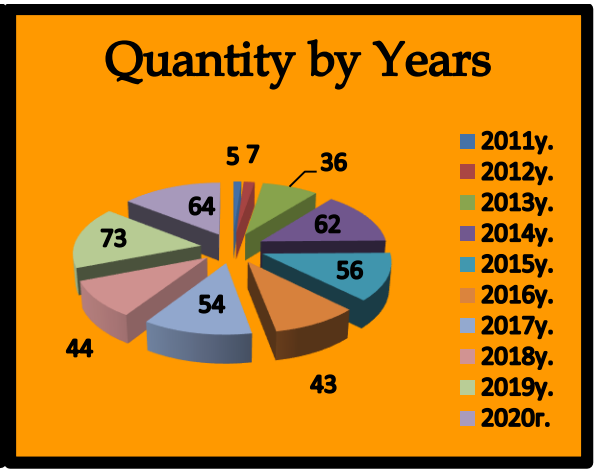


Figure 2: Distribution by year

The % distribution of patients over a 10-year period shows a significant increase in enrolment after the second year and a sustained stagnation of +- 2% over the remaining period (Figs. 3, 4).

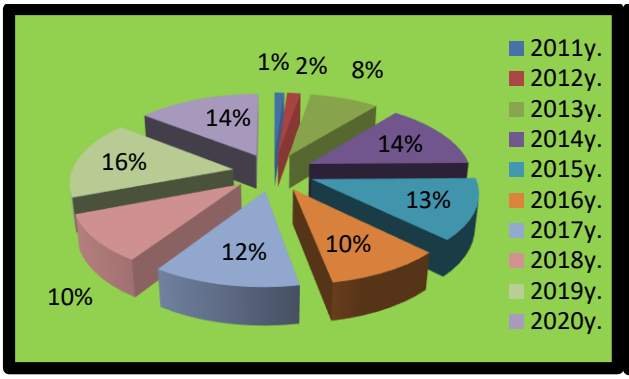


Figure 3: Distribution by year

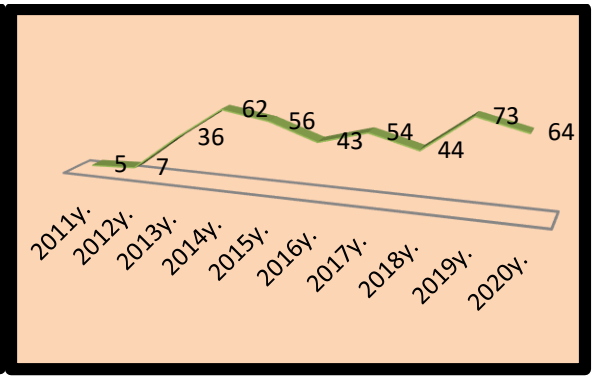


Figure 4: Curves over a 10-year period

Patients were divided into eight age groups with an interval of 10 years. The youngest was 27 years old and the oldest was 91 years old. The mean age was 67.5 years. It can be seen that three age groups had the highest number of distribution, more than 80%. These were the patients between 50 and 80 years (Fig. 5).

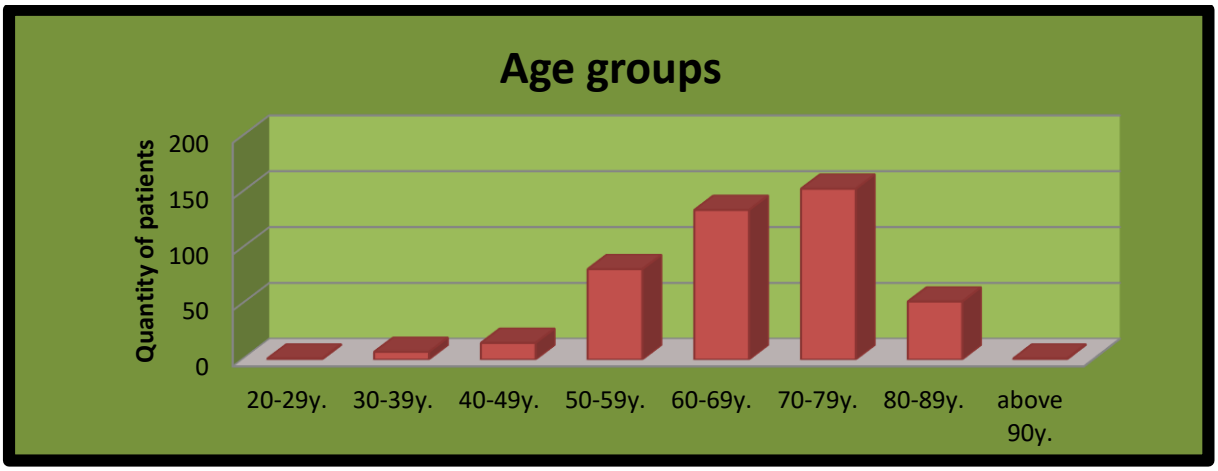


Figure 5: Age distribution

Patients were consulted and approved or rejected by a multidisciplinary team- urologist, medical oncologist, radiotherapist, imaging specialist, pathologist and anesthesiologist.

The PhD student was part of the multidisciplinary team and was actively involved in patient selection, treatment and follow-up.

2.1. Criteria for inclusion in the study

2.1.1.Detected by imaging (ultrasound, CT, MRI and PET-CT) urothelial carcinoma of the bladder.

2.1.2.Urethral urothelial carcinoma of the bladder detected by white light urethrocystoscopy and NBI.

2.1.3. Patients with evidence of microscopic or macroscopic hematuria.

2.1.4. Patients following a TUTUR.

2.1.5. Patients after postoperative intravesical chemotherapy and/or immunotherapy.

2.1.6. Patients evaluated for treatment with low-dose high-focus radiotherapy.

2.1.7. Patients with comorbidity.

2.1.8 Patients in risk groups and with harmful habits (smoking).

2.2.Exclusion criteria in the study

2.2.1. Patients with stage II and III bladder cancer.

2.2.2. Patients with active urinary tract infection at hospitalization.

2.2.3. Patients with disorder in haemostasis.

2.2.4. Patients with decompensated cardiac, hepatic and renal failure.

2.2.5. Other contraindications to general and wire anaesthesia.

3.Research methods

3.1.Sources of information

We used the following sources of information for the inclusion of patients: personal data of the group, medical records (epicrises, outpatient examinations, dispensary examinations).

3.2. Statistical methods

Data processing, analysis of the obtained results and their graphical presentation were performed using Office 2019 for Windows 10.SPSS and PSPP statistical programs.

3.2.1. Descriptive methods

. Frequency analysis of qualitative variables

. Variance analysis of quantitative variables

. Graphical analysis

3.2.2. Methods for hypothesis testing

. Parametric T-test for two samples

. Non-parametric

.. Kolmogorov.Smirnov and Shapiro-Wilk test

..Chi-square test or Fisher's exact test to search for dependencies

3.2.3. Correlation methods

. Parametric coefficient of linear correlation-Pearson

. Non-parametric linear correlation coefficient-Spierman

3.3. Diagnostic methods

3.3.1. Non-invasive diagnostic methods

- Haematological, biochemical, haemostatic, ionogram and tumour markers

- Urine - standard examination, uroculture, cytological examination

- ECG and lung and heart radiography

- Ultrasonography of abdomen and pelvis

- Whole Body CT

- MRI with multiparametric analysis at individual discretion

- PET-CT at individual discretion

3.3.2. Invasive diagnostic methods

- Urethrocystoscopy with white and NBI light

- Bladder biopsy

3.4. Operative methods of treatment

We used one of the three methods of monopolar, bipolar, or laser resection to remove bladder tumors on the entire group of 444 patients. The approach to the different surgical methods was strictly individual.

The operating room for surgical resection was equipped according to the Operating Room type. The devices we used were Karl Storz urethrocystoscope and resectoscope with passive and active elements

for monopolar and bipolar resection and Olympus -short and long resectoscope for bipolar resection.

3.4.1. Monopolar resection

Monopolar resection is the first of the surgical methods for transurethral removal of bladder tumors. Over the years, various manufacturers of resectoscopes have created safe and efficient endourological instruments. Monopolar electroresection uses a variable electrode to apply energy to the tissue of interest. The current is then passed through the patient to a return pad and then back to the generator to close the circuit. The efficiency and versatility of monopolar electrosurgery makes it the most commonly used option. This type of surgery offers a variety of electrical waves that have different tissue effects. In the monopolar procedure, an electrode is used to cut tissue and/or coagulate bleeding.

3.4.1.1. Equipment

- Karl Storz and Olympus monopolar resectoscope with 4 mm. telescope (0º,12º,30º r 70º), external and internal shrouds that prevent mixing of the irrigation-aspiration fluid, passive and active working elements and different electrodes for resection and coagulation (Fig.1). For the irrigation fluid, we used distilled water and 3% Sorbitol/Mannitol solution.

Figure 1. Olympus monopolar resection system

3.4.1.2. Technique

The operational technique used by us in performing TMR goes through the following stages:

1. Intrusion into the bladder followed by viewing with white and NBI light.
The patient is supine in the gynaecological position. After treating the operative field with disinfectant, a TUR SET is inserted. The urethra and bladder were penetrated with a 12º or 30º cystoscope. The two ureteral ostiums that excrete urine were found. With oncological guidance, all bladder walls and the bladder neck were examined with white and NBI light and the tumor lesions were found.
2.Resection of the tumor formation in parts or en bloc to healthy tissue.
After finding the tumor formation with the resectoscope, with passive or active elements, resection and coagulation was started. The tumor was resected from top to bottom and from lateral to medial in parts or en bloc. The bevels are about 5mm. The irrigation system used prevents bladder overfilling and continuously washes away the resected surface with very good visibility (Fig. 2).

3.Resection of healthy tissue around the tumor and base.

Resection of about 5mm. from the tumor lesion and resection in depth from the base of the tumor. The aim is to achieve local tumour control and to establish in-depth whether there is muscle layer involvement (Fig. 3).

4.Aspiration of the tumor resection.

The resected tumor tissue is aspirated with a 200ml glass syringe. To a clear wash and the entire resection is sent for histological examination

5.Coagulation of the resected surfaces

The resected surfaces are coagulated with a roller or "sponge" type electrode for haemostasis and smoothing of the resected surfaces.

6.Inspection of the bladder

Inspection of the bladder after surgical intervention aims to stop bleeding vessels, not to miss tumor lesion, not to miss iatrogenic damage with or without bladder wall perforation.

7.Placement of an uretheral catheter and start of irrigation

Irrigation with different droplet intensities depending on the degree of hematuria is started through an inserted 22 or 24 size three-way catheter.

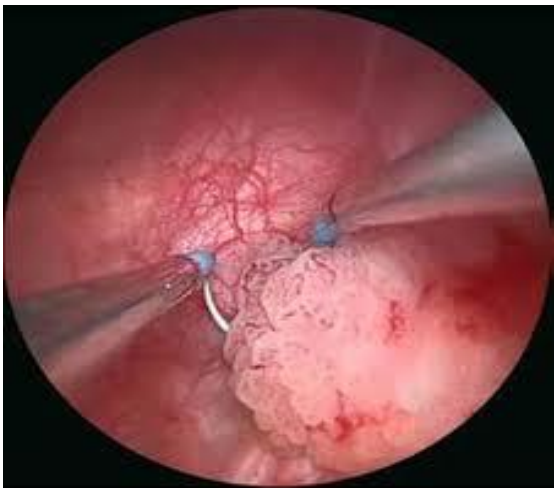


Figure 2. Papillary resection

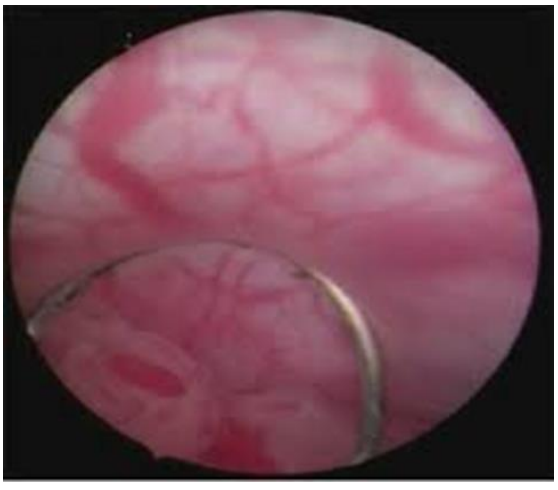


Figure 3. Resection of peritumoral tissue

3.4.2. Bipolar resection

Bipolar resection was introduced to reduce the risk of bladder perforation due to stimulation of the n.obturatorius and to obtain better resected specimens for the pathologist. In bipolar electroresection, a permanent electrode is used to apply energy to the involved tissue. This type of surgery offers a variety of electrical waves that have different tissue effects. The creation of plasma is at the base of cutting and coagulation. Plasma vaporization reduces bleeding and has an excellent local tumor response.

3.4.2.1. Equipment

- Bipolar resectoscope of Karl Storz and Olympus with 4 mm. telescope (0º,12º,30º and 70º), external and internal shroud, which do not allow mixing of the irrigation-aspiration fluid, active working element and different electrodes for resection and coagulation (Fig. 4, 5, 6). For the irrigation fluid, we used a 0.9% NaCl solution warmed to 37º.

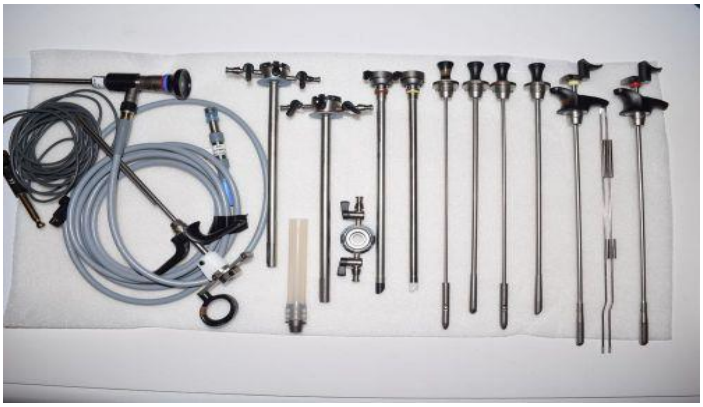
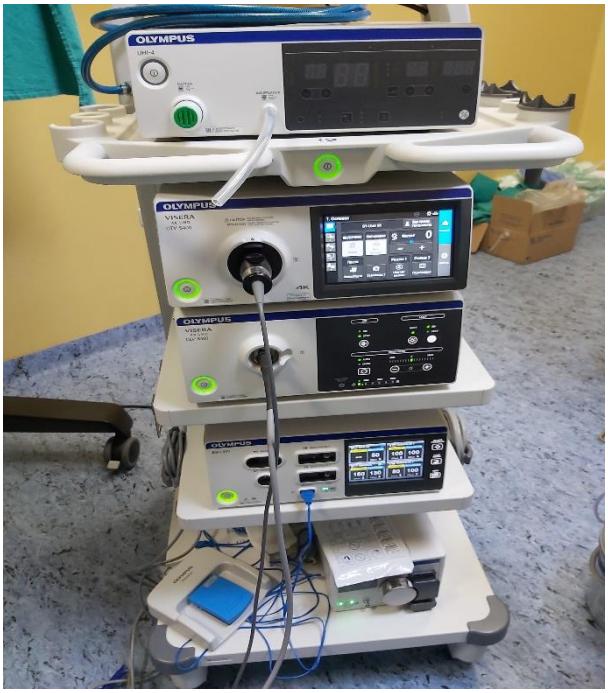


Figure 4. Toolkit



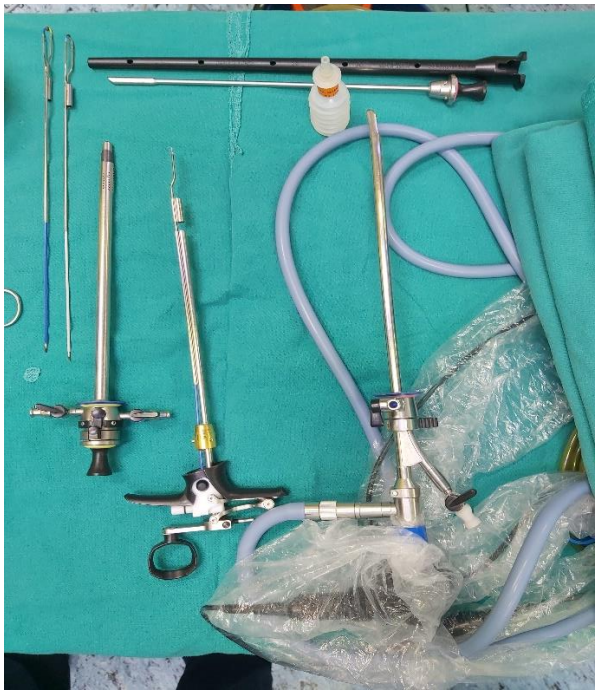


Figure 5. Olympus system

Figure 6. Bipolar resectoscope

3.4.2.2. Technique

The operating technique used by us in the performance of TMR, passes through the following stages:

1.Insertion into the bladder and view with white and NBI light

The patient was supine in the gynecological position. After treating the operative field with disinfectant, a TUR SET was inserted. The urethra and bladder were penetrated with a 12º or 30º cystoscope. The two ureteral ostiums, which secrete urine, were found. Oncologically, all the bladder and bladder neck walls were examined with white and NBI light and the tumor lesions were found.

2.Resection of the tumor formation in parts or en bloc to healthy tissue

After the tumor formation was identified with an active element resectoscope, resection and coagulation was started.The tumor was resected from top to bottom and lateral to medial in parts or en bloc.The bevels were about 5mm.The irrigation system used prevented the bladder from overfilling and continuously washed the resected surface with very good visibility (Fig. 7).

3.Resection of healthy tissue around the tumor and base

Resection of about 5mm.from the tumor lesion and resection in depth from the base of the tumor. The aim is to achieve local tumour control and to determine in depth whether there is muscle layer involvement (Fig. 8, 9).

4.Aspiration of the tumour resection

The resected tumor tissue is aspirated with a 200ml glass syringe. Till clear wash and the whole resection is sent for histological examination

5.Coagulation of the resected surfaces

The resected surfaces are coagulated with a roller or "sponge" type electrode for haemostasis and smoothing of the resected surfaces.

6.Inspection of the bladder

Inspection of the bladder after surgical intervention aims to stop bleeding vessels, not to miss tumor lesion, not to miss iatrogenic injury with or without bladder wall perforation.

7.Placement of uretheral catheter and start of irrigation

Irrigation with different droplet intensities depending on the degree of hematuria is started through an inserted 22 or 24 size three-way catheter.

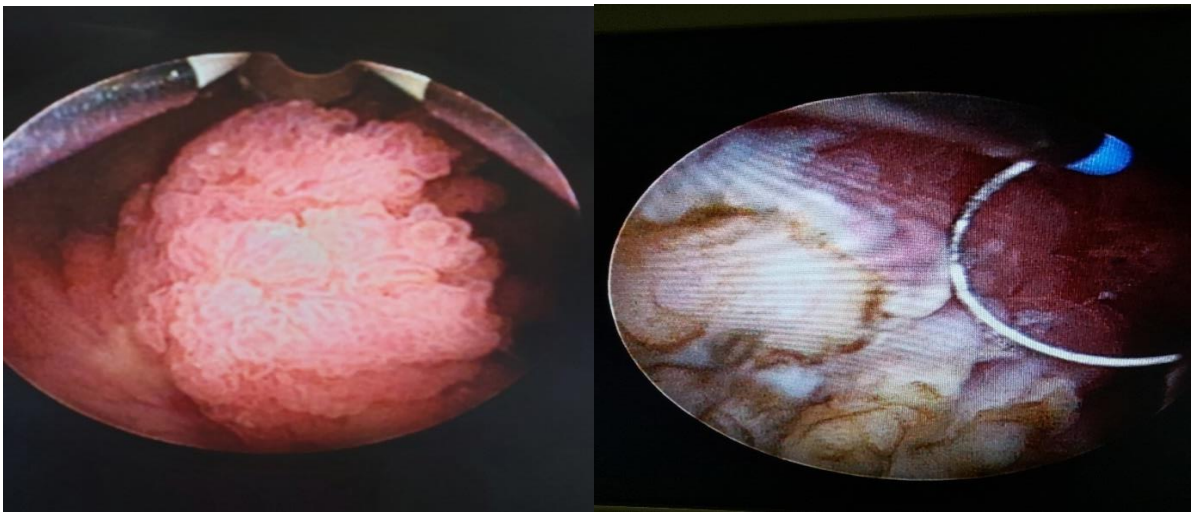


Figure7. Bipolar resection and coagulation

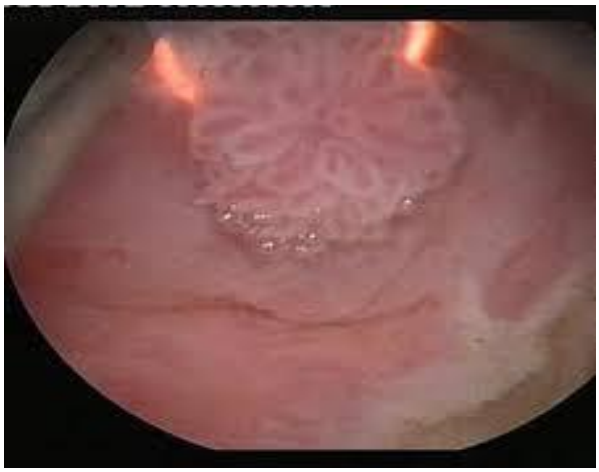


Figure 8. En-block resection

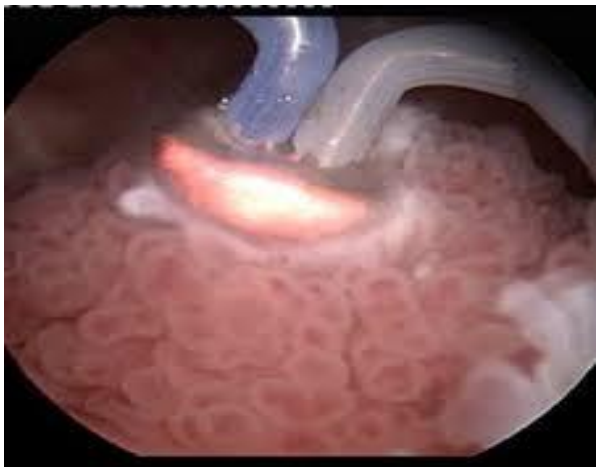


Figure 9. Plasma vaporization

3.4.3. Laser resection

En-bloc resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser is possible in selected exophytic tumors. The technique chosen depends on the size and location of the tumor and the surgeon's experience. Laser surgery is safer and more effective in TURBT. Laser

techniques without deep penetration cause less pain and bleeding. In addition, the power of the laser can be adjusted according to the size of the tumor.

The Holmium:YAG laser is a pulsed laser that emits light at 2100 nm. It combines the properties of carbon dioxide and neodymium:YAG lasers, providing both tissue cutting and coagulation in one device. Since the wavelength of the holmium can be transmitted down the optical fibers, it is particularly suitable for endoscopic surgery. The holmium wavelength is strongly absorbed by water. Tissue ablation is performed superficially, providing a precise incision with a thermal zone of injury ranging from 0.5 to 1.0 mm. The holmium laser produces vapor bubbles at the tip of the fiber, separating the tissue layers, tearing and coagulating them into small and medium sections 2-3 mm deep. This level of coagulation is sufficient for adequate hemostasis. The Holmium:YAG laser is a multipurpose surgical laser. Its use in urology is expected to increase over time as a result of these characteristics.

3.4.3.1. Equipment

HoL-EBRBT was performed with a 30 W Holmium laser system (MegaPulse 30+ Holmium YAG Laser-System from Richard Wolf) using a 275 micron fiber using a 26 F resectoscope (Olympus, Germany) (Figs. 10, 11). Saline was used in all cases.

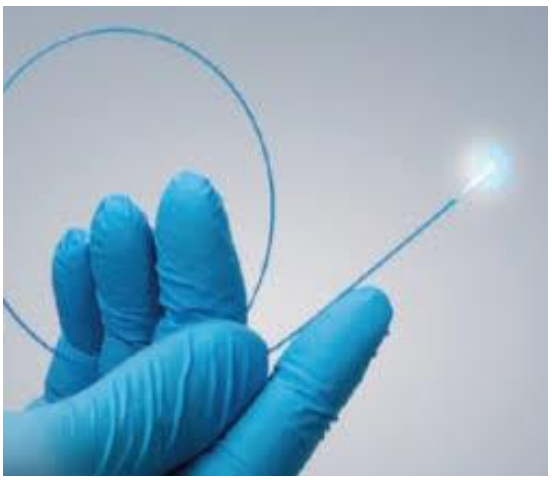


Figure 10. Wolf laser system

Figure 11. Laser fiber 275 μm

3.4.3.2. Technique

The operational technique used by us in performing TMR goes through the following stages:

1.Intrusion into the bladder and view with white and NBI light

The patient is supine in the gynaecological position. After treating the operative field with disinfectant, a TUR SET is inserted. The urethra and bladder were penetrated with a 12º or 30º cystoscope. The two ureteral ostiums,which excrete urine, were found. With oncological guidance, all bladder walls and bladder neck were examined with white and NBI light and the foot tumor lesion was found.

2. Resection of the tumor formation en bloc to healthy tissue

Once the tumor formation was identified, the tumor "leg" was resected and coagulated with a 275 micron active element snotic fiber resectoscope with a power of 14.4W (Fig. 12).

3. Aspiration of the tumor resectate

The resected tumor tissue is aspirated with a 200 ml glass syringe. Till clear wash comes out and the whole resection is sent for histological examination.

4. Coagulation of the resected surfaces

The resected surfaces are coagulated with a roller or sponge type electrode for haemostasis and smoothing of the resected surfaces.

5. Inspection of the bladder.

Inspection of the bladder after surgical intervention aims to stop bleeding vessels,not to miss a tumor lesion,not to miss iatrogenic damage with or without perforation of the bladder wall.

6.Placement of urethral catheter and start of irrigation

Irrigation with different droplet intensities depending on the degree of hematuria is started through an inserted 22 or 24sh three-way catheter.

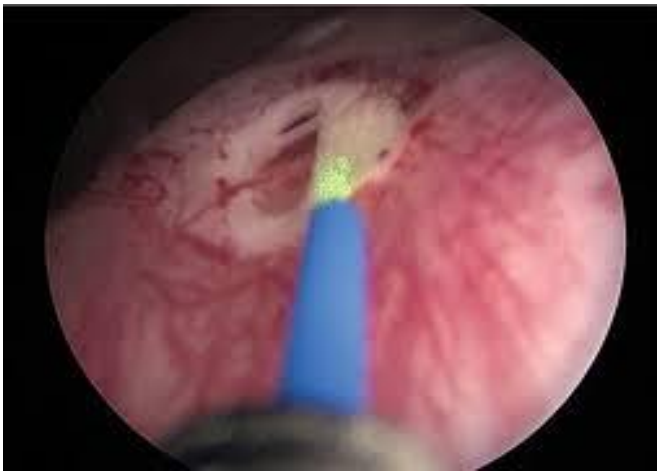


Figure 12. Laser resection en-block

3.5. Conservative methods

Operative removal of the tumor is only the initial stage of a multidisciplinary approach to the treatment of superficial urothelial carcinoma of the bladder. Local chemotherapy and/or immunotherapy have entered the guidelines for decades, aimed at reducing the occurrence of new recurrences and halting disease progression. Current treatment of urothelial carcinoma is complemented by the use of linear accelerator radiotherapy. Systemic immunotherapy, intake of drugs with proven antitumor effect and diet are new steps in the treatment of recurrent urothelial carcinoma.

3.5.1. Intravesical therapy

Intravesical chemotherapy or immunotherapy is a subsequent stage of the multimodal approach to the treatment of superficial bladder cancer. Mitomycin

20mg and 40mg, Epirubicin 50mg and Bacilus Calmette-Guérin (BCG) are used worldwide. Intravesical infusions of Mitomycin, Epirubicin, or BCG were performed using a size 16 non-Latentine catheter. The time without urination was between 100 and 150 min, averaging 120 min. The course of treatment was 6 weeks, once a week with a follow-up course of 6 months once a month. Prior to each intravesical therapy, patients underwent full bloud count, urea, creatinine, urine and ultrasonography of abdominal organs and pelvic floor.

3.5.1.1. Mitomycin 40mg.

Mitomycin is an antitumor antibiotic that inhibits DNA synthesis by creating DNA cross-links that stop cell replication and ultimately cause cell death. Because cancer cells generally divide faster and with less error correction than healthy cells, they are more sensitive to this damage.

This cell damage slows or stops the growth of cancer cells in the body.

3.5.1.2. Epirubicin 50mg.

Epirubicin is an anthracycline cytotoxic agent. It is known that anthracyclines can affect a number of biochemical and biological functions in eukaryotic cells. The exact mechanisms of cytotoxicity and/or antiproliferative properties of epirubicin are not fully understood.

3.5.1.3. BCG

BCG has been used to treat non-muscle invasive bladder cancer for more than 30 years. It is one of the most successfully used molecules for cancer biotherapy. Despite the long clinical experience with BCG, the mechanism of its therapeutic effect is still under investigation. Available data suggest that urothelial cells and immune system cells play a crucial role in the therapeutic antitumor effect of BCG. Immune system cells that have a potential role in BCG therapy include CD4+ and CD8+ lymphocytes, natural killer cells, granulocytes,

macrophages and dendritic cells. Bladder cancer cells are killed by direct cytotoxicity from these cells, by secretion of soluble factors such as TRAIL (tumor necrosis factor binding apoptosis-inducing ligand) and to some extent by the direct action of BCG.

3.5.2. High-focused radiotherapy

Modern use of a linear accelerator for radiotherapy reduces the risk of recurrence and improves quality of life. Radiotherapy has been used to treat cancer patients for 100 years. The goal of radiation is to remove the tumor while preserving the structure and function of surrounding normal tissues. Tumor cells are less able than normal cells to repair DNA breaks that are produced by radiation. These DNA breaks cause a cascade of downstream molecular events that eventually lead to cell death. Medical Linear Accelerators (Linacs) are cyclic electron accelerators to kinetic energies of 4 to 25 MeV using non-conservative microwave radio frequency fields on the order of 103 MHz (L range) to 104 MHz (X range), and a traveling wave frequency of 2856 MHz (S range).

For our patients, we used an ELEKTA linear accelerator (Figs. 13, 14). The absorbed daily dose was 1.8Gy up to a total absorbed dose of 50-60 Gy. Radiotherapy was performed with a linear accelerator with directed beam photon emission. CT scan with percutaneous marking of the irradiated volume was performed in all patients (Fig. 15). Weekly full blood count, urea, creatinine, urine and ultrasonography were performed for the presence of retention or hydronephrosis. During the course, patients were with an urethral catheter.

Figure 13. ELEKTA linear accelerator

Figure 14. Radiosurgery room

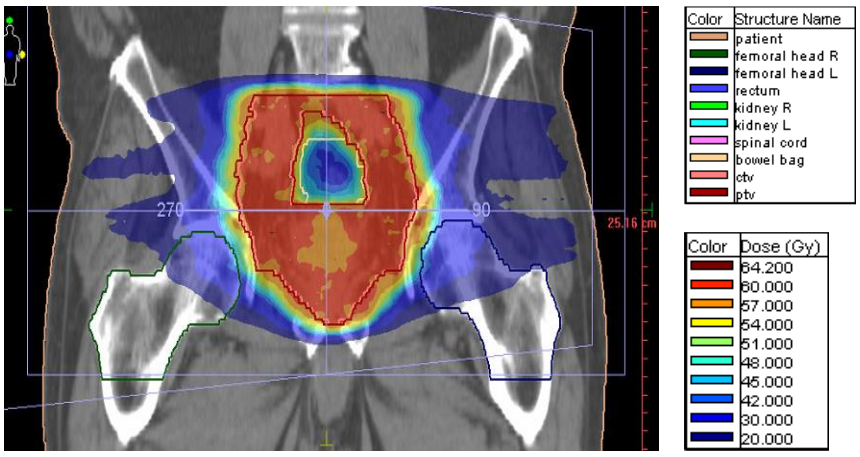


Figure 15. Radiotherapy plan

3.5.3. Immunotherapy

For systemic immunotherapy, we used pembrolizumab. It is a monoclonal antibody that helps to restore the body's immune system to fight cancer. It creates its anti-cancer effects by blocking a specific protein used by cancer cells called PD-L1 to avoid attacks by the immune system. Once PD-L1 is blocked, immune system cells can identify cancer cells as a threat and initiate an attack to destroy the cancer formation. Immunotherapy significantly reduces the risk of bladder cancer recurrence while increasing the percentage of patients who receive a complete response after surgery. Immunotherapies used for bladder cancer "train" the body's immune system to recognize cancer cells. The dose administered is 200mg every 3 weeks.

3.5.4. Nutrition in urothelial carcinoma

A reduced risk of bladder cancer has been found in non-smokers with a high daily intake of cruciferous vegetables (cabbage, Brussels sprouts, broccoli and cauliflower). It is assumed that the protective effect of vegetables in this family is most likely due to the high concentration of carotenoids, lutein and zeaxanthin in them. In vitro studies have shown that isoflavonoids found in soybeans can inhibit the development of transitional cell carcinoma cell cultures. According to some authors, milk intake reduces the risk of developing carcinoma, although according to others, no convincing evidence has been found to support a direct link between milk or dairy intake and high risk. The role of various micronutrients, including vitamin E, carotenoids, vitamin D, thiamine and niacin in relation to the risk of developing endothelial tumours warrants further large-scale studies, particularly in relation to high-risk groups such as heavy smokers and elderly patients. The trace element selenium has not been shown to have protective properties, but it has been shown that people with high plasma selenium levels have a relatively lower incidence of developing the disease. Regarding the preventive effect of non-steroidal anti-inflammatory drugs (NSAIDs), data are conflicting although the incidence is lower among patients taking analgesics.

The main aim of nutritional treatment in patients with urothelial carcinoma is to help to carry out the planned active treatment without interruption and to restore normal and healthy nutrition rapidly to avoid malnutrition, loss of muscle mass, development of a catabolic state and immunodeficiency. The benefits of optimal nutrient and caloric intake in patients undergoing active treatment and in the recovery period are well known and documented. The assessment of nutritional status should take into account not only the patient's needs but also his/her quality of life and expectations, and a dietary plan should be developed on this basis.

3.5.5. Healthy lifestyle

1. Regular physical activity - physical activity is essential for controlling and maintaining optimal body weight and reduces the risk of developing a number of malignancies. Moderate and/or vigorous exercise, for at least 30 min daily on most days of the week, has additional benefits.

2. Avoiding overweight and weight gain in adulthood - increased caloric intake underlies fat accumulation and is a major risk factor for cancer development. Taking statins in patients with hypercholesterolaemia reduces the risk of developing bladder cancer.

3. Limiting alcohol and cigarette consumption - alcohol and tobacco consumption is a risk factor for the development of a number of cancers as well as accidents and leads to addiction, although low to moderate consumption reduces the risk of coronary heart disease, however both family history and individual preferences should be taken into account.

4. Fruit and vegetable consumption - fruit and vegetable intake in adults probably does not have a major impact on cancer incidence, but it does reduce the risk of developing cardiovascular disease.

5. Eating whole grains and avoiding refined carbohydrates and sugar - regular consumption of whole grain products instead of refined flour and sugar reduces the risk of developing cardiovascular disease and diabetes. The effect on the risk of developing cancer is not fully understood.

6. Replace red meat and dairy products with fish, nuts and legumes - red meat consumption increases the risk of developing colon cancer, diabetes and coronary heart disease and should therefore be limited. Excessive consumption of dairy products increases the risk of developing prostate cancer. Fish, nuts and legumes are valuable sources of mono- and polyunsaturated fats and plant proteins and lead to a lower incidence of cardiovascular disease and diabetes.

7. Discussing the intake of vit. D - a significant proportion of the population, especially those living at higher latitudes have suboptimal levels of Vit. D. A large proportion of the adult population may benefit from an additional 1000 UI of Vit. D especially during periods of reduced sunshine. Additional intake of Vit. D intake will at least reduce the risk of bone fractures, and possibly reduce the incidence of colorectal cancer and also bladder cancer.

IV. Results

1. To develop an algorithm for selecting patients suitable for transurethral resection

Patients were divided into several groups according to tumor localization, degree of differentiation, tumor size, multifocality, comorbidity, and statin intake. All patients underwent the mandatory clinical minimum of laboratory investigations, abdominal ultrasonography on POS, white light and NBI urethrocystoscopy.

1.1. Tumor localization group

In the first group, patients were selected and distributed according to the localization of the tumor process.It is evident that lateral wall,posterior wall and tumors with more than one localization accounted for more than 50% of all other localizations (Fig. 6).

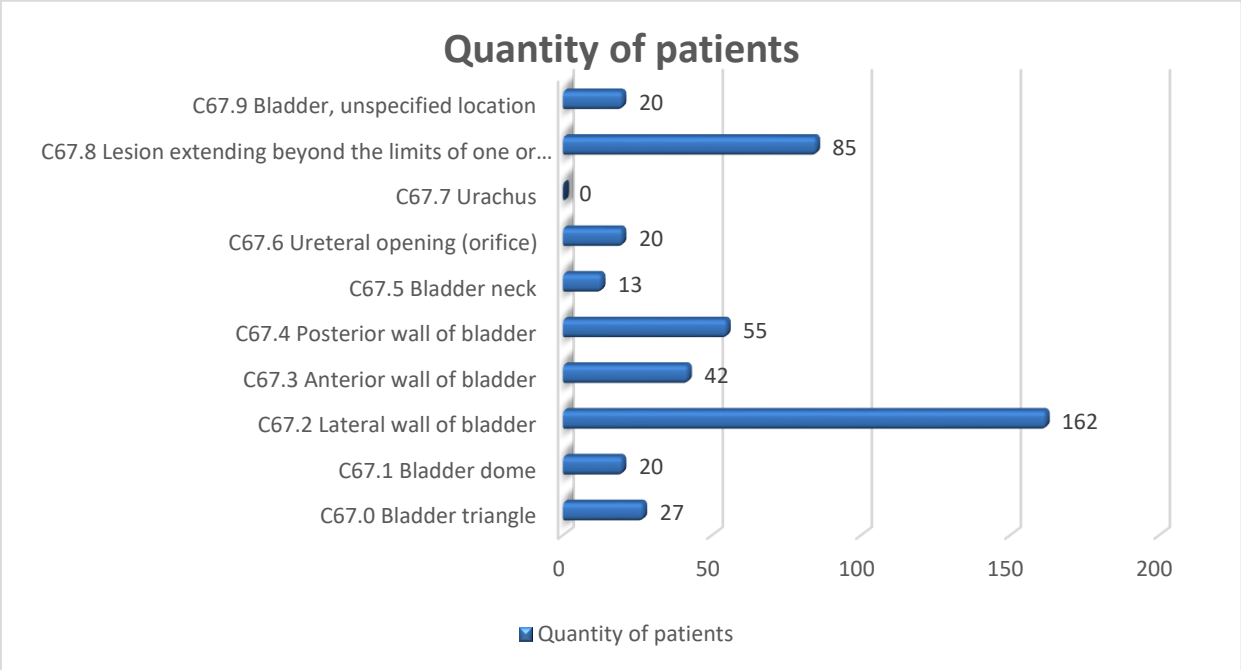


Figure 6: Number of patients by tumor localization

The percentage distribution by sex and localization can be seen.In both sexes lateral wall was the most frequent localization (Table 1).

C67					
		Frequency	*Percent*	*Valid Percent*	*Cumulative Percent*

Valid	C67.0	6	1.4%	1.4%	1.4%
	C67.1	3	.7%	.7%	2.0%
	C67.2	29	6.5%	6.5%	8.6%
	C67.3	9	2.0%	2.0%	10.6%
	C67.4	14	3.2%	3.2%	13.7%
	C67.5	4	.9%	.9%	14.6%
	C67.6	4	.9%	.9%	15.5%
	C67.8	23	5.2%	5.2%	20.7%
	C67.9	6	1.4%	1.4%	22.1%
	C67	1	.2%	.2%	22.3%
	C67.0	21	4.7%	4.7%	27.0%
	C67.1	17	3.8%	3.8%	30.9%
	C67.2	132	29.7%	29.7%	60.6%
	C67.3	33	7.4%	7.4%	68.0%
	C67.4	40	9.0%	9.0%	77.0%
	C67.5	9	2.0%	2.0%	79.1%
	C67.6	16	3.6%	3.6%	82.7%
	C67.8	63	14.2%	14.2%	96.8%
	C67.9	14	3.2%	3.2%	100.0%
Total		444	100.0%		

Table 1. Frequency-descriptive analysis for distribution by localization

More than 1/3 of the tumor localization is on the lateral wall, increasing the risk of obturator syndrome when the lesions are resected (Fig. 7).

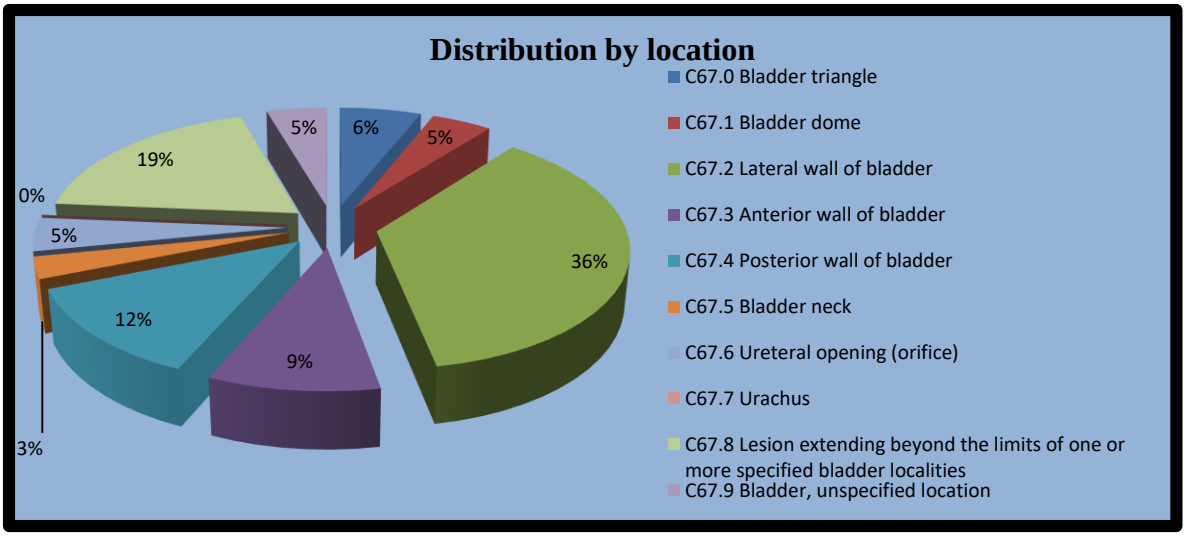


Chart 7: Percentage distribution by location

1.2 Differentiation groups

Patients were divided into three groups according to tumor differentiation. Pathological verification was performed by videomicroscope and in case of

discordant tumors by immunohistochemical analysis. More than 50% had highly differentiated urothelial carcinoma (Table 2).

G1- Highly-differentiated (PUNLMP)	226	51%
G2- Moderately-differentiated (LG)	181	41%
G3- Low-differentiated (HG)	37	8%

Table 2. Distribution by degree of differentiation

The following table shows a correlation analysis by gender and degree of differentiation (Table 3, Fig. 8).

SEX	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
						Lower Bound
G1	0	173	1	0	0	1
	1	53	1	0	0	1
	Total	226	1	0	0	1
G2	0	144	1	0	0	1
	1	37	1	0	0	1
	Total	181	1	0	0	1
G3	0	25	1	0	0	1
	1	12	1	0	0	1
	Total	37	1	0	0	1

Table 3. Gender distribution and differentiation

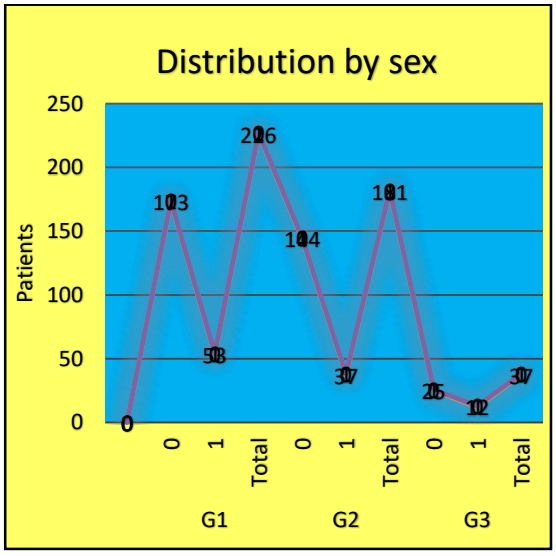


Figure 8: Gender distribution

1.3 Groups by tumor size

Patients were divided into three groups according to the size of the tumor lesion. More than 50% had a tumor of 1 to 2 cm with a papillary pattern (Table 4).

Tumour size	Quantity of patients
0-1 cm.	137
1-2 cm.	232
above 2 cm.	73

Table 4. Distributed by tumor size in cm.

More than 75% of the lesions were papillary with a narrow or broad base and 25% with solid growth escalating toward the lumen. More than 20% of patients had tumors larger than 3 cm with rough papillary architecture and surfaces with ulceration and necrosis. There were patients with calcium deposits on the tumor surface and evidence of chronic inflammation.

In patients with tumor formation up to 2cm.the male/female ratio was 3/1. In tumors over 2cm this ratio is 4/1 (Tables 5, 6, 7).

			SEX		*Total*
			0	*1*	
Up to 1cm..	*1*	*Count*	*100*	*37*	*137*
		Row %	*73.00%*	*27.00%*	*100.00%*
		Column %	*100.00%*	*100.00%*	*100.00%*
		Total %	*73.00%*	*27.00%*	*100.00%*
Total		*Count*	*100*	*37*	*137*
		Row %	*73.00%*	*27.00%*	*100.00%*
		Column %	*100.00%*	*100.00%*	*100.00%*
		Total %	*73.00%*	*27.00%*	*100.00%*

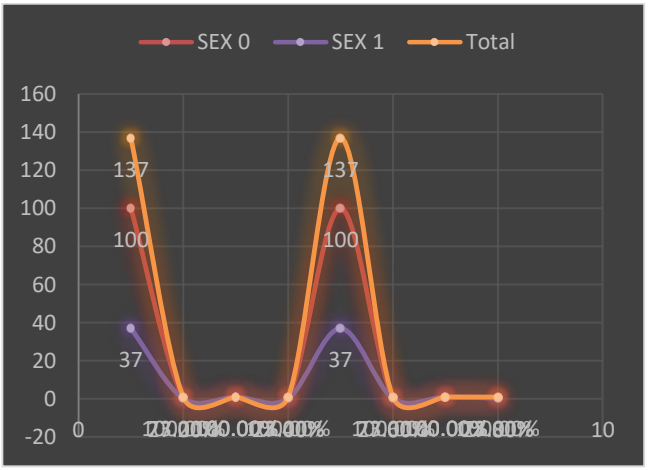


Table 5. Frequency distribution of tumors up to 1 cm by sex

			SEX		Total
			0	1	
1-2cm.	1	Count	179	53	232
		Row %	77.20%	22.80%	100.00%
		Column %	100.00%	100.00%	100.00%
		Total %	77.20%	22.80%	100.00%
Total		Count	179	53	232

	Row %	77.20%	22.80%	100.00%
	Column %	100.00%	100.00%	100.00%
	Total %	77.20%	22.80%	100.00%

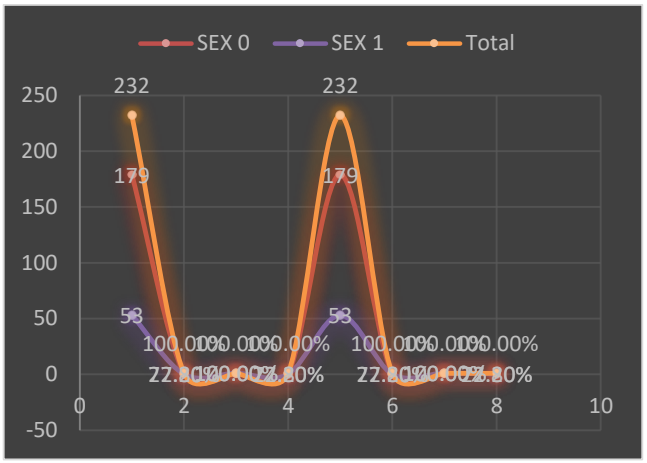


Table 6: Frequency distribution of tumors up to 2 cm by sex

			SEX		Total
			0	1	
Above 2cm.	1	Count	62	11	73
		Row %	84.90%	15.10%	100.00%
		Column %	100.00%	100.00%	100.00%
		Total %	84.90%	15.10%	100.00%
Total		Count	62	11	73
		Row %	84.90%	15.10%	100.00%
		Column %	100.00%	100.00%	100.00%
		Total %	84.90%	15.10%	100.00%

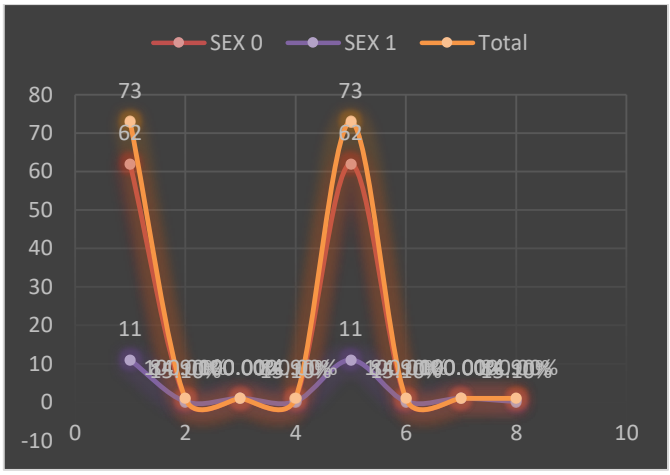


Table 7: Frequency distribution of tumors over 2 cm by sex

1.4 Multifocality Groups

About half of those operated on had multiple tumours. The distribution of lesions was of more than two localisations. The tumors were of different sizes and some with varying degrees of differentiation (Table 8). Of these, 20% had more than 10 or more lesions.

Quantity of tumors	Quantity of patients
Single tumours	235
Multiple tumours	209

Table 8: Distribution by multifocality

In women, the rate of multifocality was 3 times lower than the male group (Table 9).

			SEX		Total
			0	1	
Multifocal	1	Count	148	61	209
		Row %	70.8%	29.2%	100.0%
		Column %	100.0%	100.0%	100.0%
		Total %	70.8%	29.2%	100.0%
Total		Count	148	61	209
		Row %	70.8%	29.2%	100.0%
		Column %	100.0%	100.0%	100.0%
		Total %	70.8%	29.2%	100.0%

Table 9. Gender distribution of multifocality

The distribution by grade of malignancy and size shows that tumors up to 2 cm and G2 have the highest % of multifocality (Table 10).

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Multifocal × G1	95	21.4%	349	78.6%	444	100.0%
Multifocal × G2	91	20.5%	353	79.5%	444	100.0%
Multifocal × G3	23	5.2%	421	94.8%	444	100.0%
Multifocal × up to 1cm.	64	14.4%	380	85.6%	444	100.0%
Multifocal × 1-2cm.	95	21.4%	349	78.6%	444	100.0%
Multifocal × above 2cm.	50	11.3%	394	88.7%	444	100.0%

Table 10. Frequency distribution by differentiation grade and tumor size

1.5 Comorbidity & Smoking Cessation Groups

Nearly 80% of the patients had comorbidities.These included diseases of the CVS, diseases of the RS, diseases of the metabolism, and diseases of the NS. active smokers (Table 11).

Criteria	Quantity of patients
Comorbidity	380
Active smokers	98

Table 11. Distributed by comorbidity and actively smoking

In (Tables 12, 13), the relationship of the presence of comorbidity and the occurrence of primary bladder cancer can be seen. The distribution of the patients according to the set criteria gives us reason to think , that with timely treatment of concomitant diseases the risk of occurrence and progression of the disease will decrease.

Descriptives									
	Comorbidity	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
SEX	0	64	.20	.41	.05	.10	.30	.00	1.00
	1	380	.23	.42	.02	.19	.28	.00	1.00
	Total	444	.23	.42	.02	.19	.27	.00	1.00
G1	0	45	1.00	.00	.00	1.00	1.00	1.00	1.00
	1	181	1.00	.00	.00	1.00	1.00	1.00	1.00
	Total	226	1.00	.00	.00	1.00	1.00	1.00	1.00
G2	0	17	1.00	.00	.00	1.00	1.00	1.00	1.00
	1	164	1.00	.00	.00	1.00	1.00	1.00	1.00
	Total	181	1.00	.00	.00	1.00	1.00	1.00	1.00
G3	0	2	1.00	.00	.00	1.00	1.00	1.00	1.00
	1	35	1.00	.00	.00	1.00	1.00	1.00	1.00
	Total	37	1.00	.00	.00	1.00	1.00	1.00	1.00
Up to 1cm.	0	22	1.00	.00	.00	1.00	1.00	1.00	1.00
	1	115	1.00	.00	.00	1.00	1.00	1.00	1.00
	Total	137	1.00	.00	.00	1.00	1.00	1.00	1.00
1-2cm.	0	33	1.00	.00	.00	1.00	1.00	1.00	1.00
	1	199	1.00	.00	.00	1.00	1.00	1.00	1.00
	Total	232	1.00	.00	.00	1.00	1.00	1.00	1.00
Above 2cm.	0	8	1.00	.00	.00	1.00	1.00	1.00	1.00
	1	65	1.00	.00	.00	1.00	1.00	1.00	1.00
	Total	73	1.00	.00	.00	1.00	1.00	1.00	1.00
Multifocal	0	42	1.00	.00	.00	1.00	1.00	1.00	1.00
	1	167	1.00	.00	.00	1.00	1.00	1.00	1.00
	Total	209	1.00	.00	.00	1.00	1.00	1.00	1.00

Table 12. Correlation between comorbidity and bladder tumors

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
SEX	Between Groups	.05	1	.05	.30	.585
	Within Groups	78.51	442	.18		
	Total	78.57	443			
G1	Between Groups	2.53E-029	1	2.53E-029	-224.00	NaN
	Within Groups	-2.53E-029	224	-1.13E-031		
	Total	.00	225			
G2	Between Groups	1.72E-029	1	1.72E-029	-179.00	NaN
	Within Groups	-1.72E-029	179	-9.59E-032		
	Total	.00	180			
G3	Between Groups	4.07E-034	1	4.07E-034	-35.00	NaN
	Within Groups	-4.07E-034	35	-1.16E-035		
	Total	.00	36			
Up to 1cm.	Between Groups	1.71E-031	1	1.71E-031	-135.00	NaN
	Within Groups	-1.71E-031	135	-1.27E-033		
	Total	.00	136			
1-2cm.	Between Groups	2.74E-029	1	2.74E-029	-230.00	NaN

	Within Groups	-2.74E-029	230	-1.19E-031		
	Total	.00	231			
Above 2cm.	Between Groups	2.19E-031	1	2.19E-031	-71.00	NaN
	Within Groups	-2.19E-031	71	-3.08E-033		
	Total	.00	72			
Multifocal	Between Groups	1.62E-029	1	1.62E-029	-207.00	NaN
	Within Groups	-1.62E-029	207	-7.82E-032		
	Total	.00	208			

Table 13. ANOVA anlysis for comorbidity

In (Table 14) we can see the correlation between smoking cessation and the occurrence of primary bladder cancer. The distribution of patients according to the set criteria gives us reason to think that smoking cessation or restriction leads to a lower risk of disease occurrence and progression. The correlation coefficient was 1.000, indicating a positive correlation.

		Smoking cessation	**G1**	**G2**	**G3**	**Up to 1cm.**	**1-2cm.**	**Up to 2cm.**	**Multifocal**
Smoking cessation	Pearson Correlation	1.000	NaN	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)		NaN	NaN	NaN	NaN	NaN	NaN	NaN
	N	442	225	180	37	137	231	72	208
G1	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN		NaN	NaN	NaN	NaN	NaN	NaN
	N	225	226	0	0	77	114	34	95
G2	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN		NaN	NaN	NaN	NaN	NaN
	N	180	0	181	0	56	98	27	91
G3	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN	NaN		NaN	NaN	NaN	NaN
	N	37	0	0	37	4	20	12	23
Up to 1cm.	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN	NaN	NaN		NaN	NaN	NaN
	N	137	77	56	4	137	0	0	64
1-2cm.	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN	NaN	NaN	NaN		NaN	NaN
	N	231	114	98	20	0	232	0	95
Above 2cm.	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN	NaN	NaN	NaN	NaN		NaN
	N	72	34	27	12	0	0	73	50
Multifocal	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN	NaN	NaN	NaN	NaN	NaN	
	N	208	95	91	23	64	95	50	209

Table 14. Pearson correlation

2. To investigate the safety of transurethral monopolar, bipolar and laser resection in patients with superficial urothelial carcinoma of the bladder

Patients were divided into three groups:

Group A-patients with monopolar resection. Group B-patients with bipolar resection. Group C-patients with laser resection. In (Table 15), patients were systematized according to groups, number, mean operative time in minutes,mean hospital stay in days,verticalized and days with a urethral three-way catheter.

Groups	Type of resection	Number of patients	Operation time in min.	Length of hospital stay in days	Verticalized in days	Days with a urethral catheter
A	Monopolar resection	102	29.43	2.52	1.26	2.54
B	Bipolar resection	319	26.88	2.44	1.17	2.48
C	Laser resection	23	25.17	2	1	2

Table 15. Distribution by type of resection

In all three groups, there were minimal differences in the survey values. All the three methods of surgical treatment were effective and safe for the patient.There was not much advantage of laser surgery over the other two methods. Patients were under general or epidural anaesthesia.The mean operative time was between 10 and 52 min. mean 27.38 min. The number of patients and the operative time can be seen (Fig. 9-11).

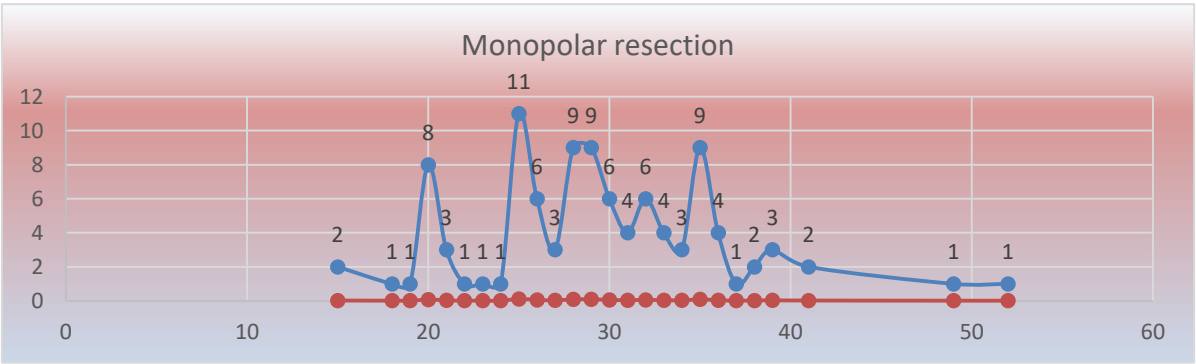


Figure 9. Patients undergone monopolar resection

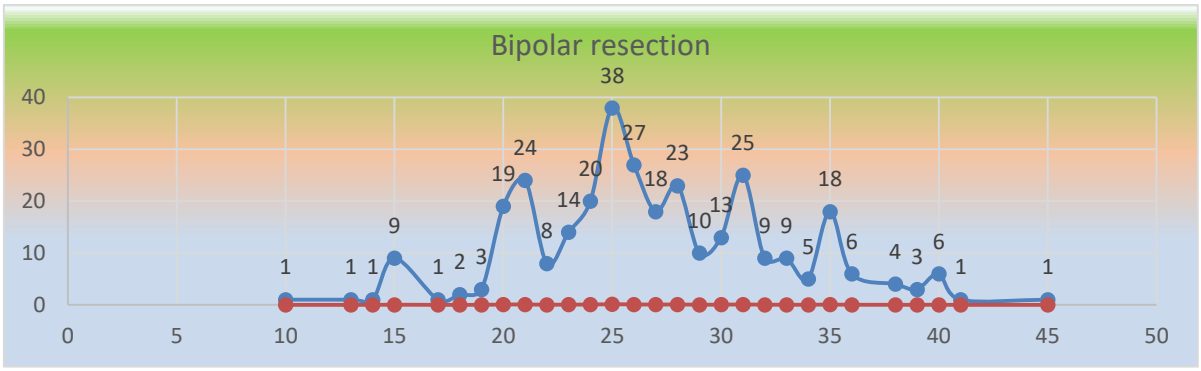


Figure 10. Patients undergone bipolar resection

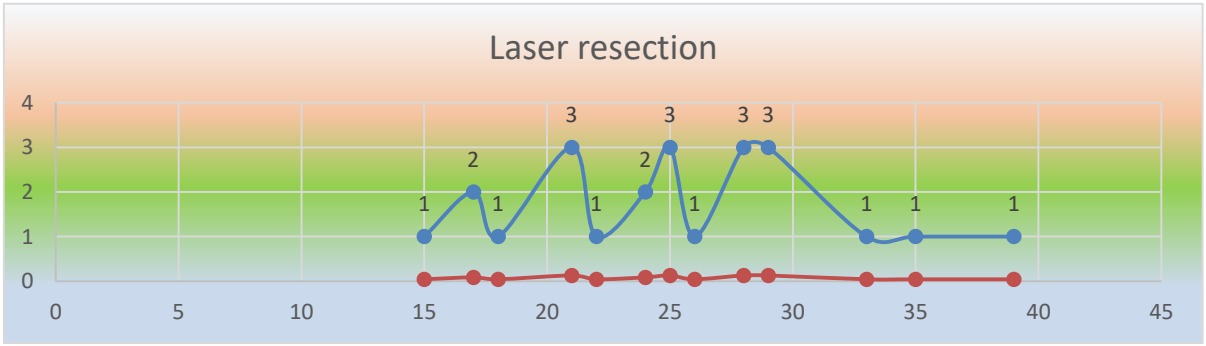


Figure 11. Patients undergone laser resection

Early ambulation in the first 24 hours and removal of the urethral catheter within 48 hours were prerequisites for a low rate of postoperative complications and a better quality of life.

The operated patients did not require delayed TUTUR.

Tumor lesions were removed in a single stage.

Patients were stratified by sex, mean age, tumor size, multifocality, and degree of differentiation (Table 16).

Groups	Sex	Quantity if patients	Age	0-1cm.	1-2cm.	Above 2cm.	Multifocal	G1	G2	G3
A	Male	83	66.5	29	40	14	36	33	40	10
A	Female	19	71.5	4	11	4	14	6	10	3
B	Male	241	68	69	125	46	103	128	99	14
B	Female	78	67	32	39	7	14	45	26	7
C	Male	18	59.4	2	14	2	9	12	5	1
C	Female	5	63.4	1	3	1	4	2	1	2

Table 16. Distribution by groups

The application of transurethral surgery remains the "gold standard "for the treatment of superficial transitional cell tumor of the bladder.

The use of bipolar and laser resection have significantly reduced the incidence of TUR syndrome and hence lesion of the urethra, bladder and prostate.

No case of intraperitoneal rupture was recorded.

Only 7 patients required haemotransfusion (1.57%) in the first 24 hours (Table 17).

haemotransfusion during surgery	0
haemotransfusion after surgery	3
significant bleeding during surgery	7
haemotransfusion after 24h.	7

Table 17. Number of patients with haemotransfusion

Several intraoperative complications occurred during the surgical intervention (Fig. 12).The bladder lesion was due to agitation of the n.obturatorius. The results are summarized and presented in graphical form.

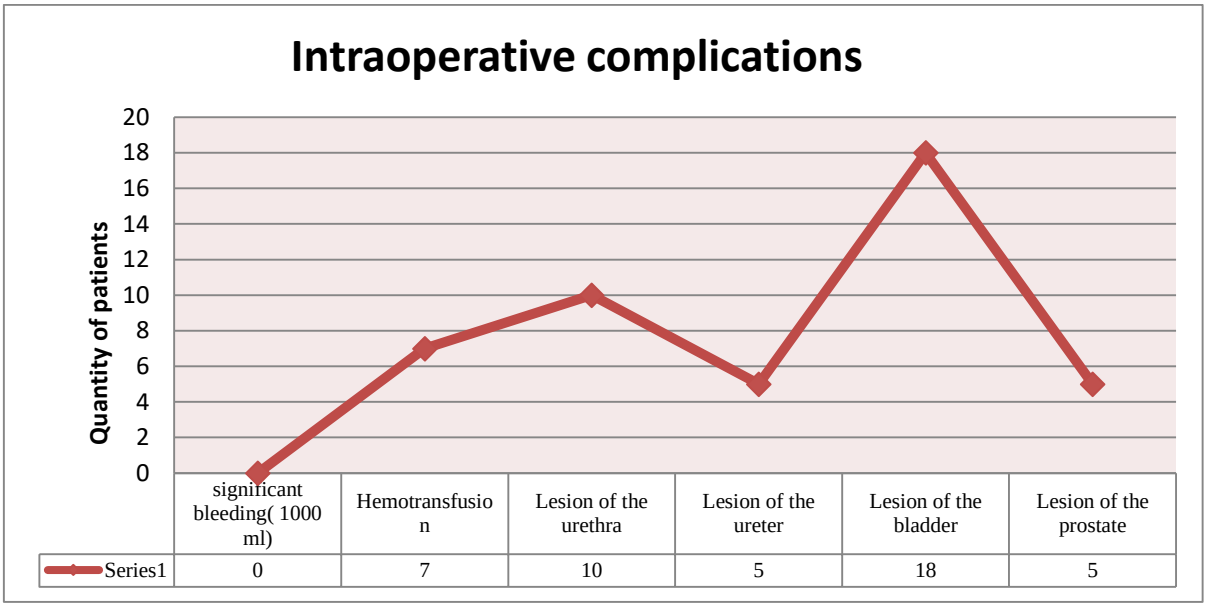


Figure 12. Intraoperative complications after TUR

The presence of early complications were tabulated and summarized in graphical form (Fig. 13). The highest proportion of hematuria was reported in early complications.

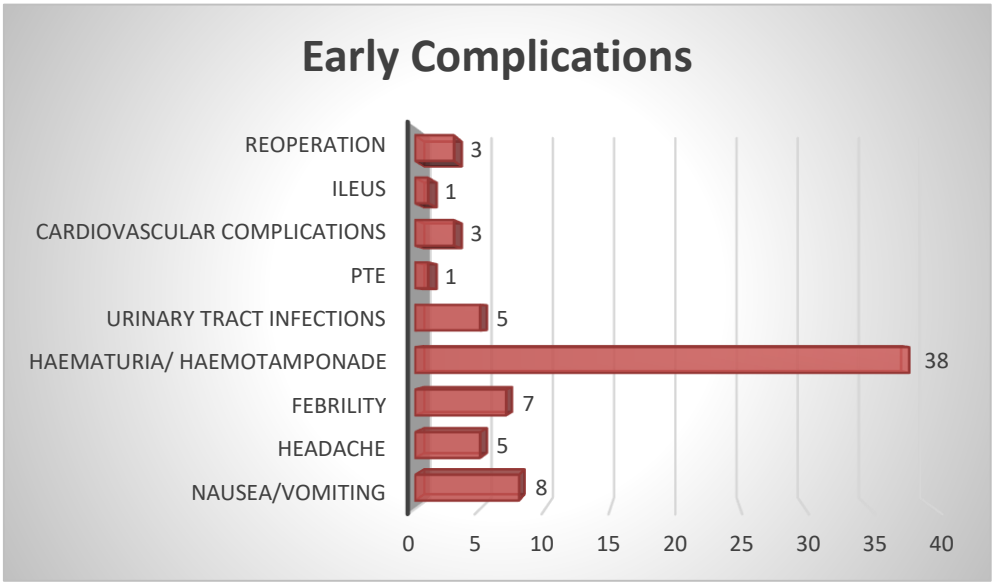


Figure 13. Early postoperative complications

The occurrence of late complications are tabulated and summarized in graphical form (Fig. 14). The highest proportion of urinary tract infection was reported in late complications.

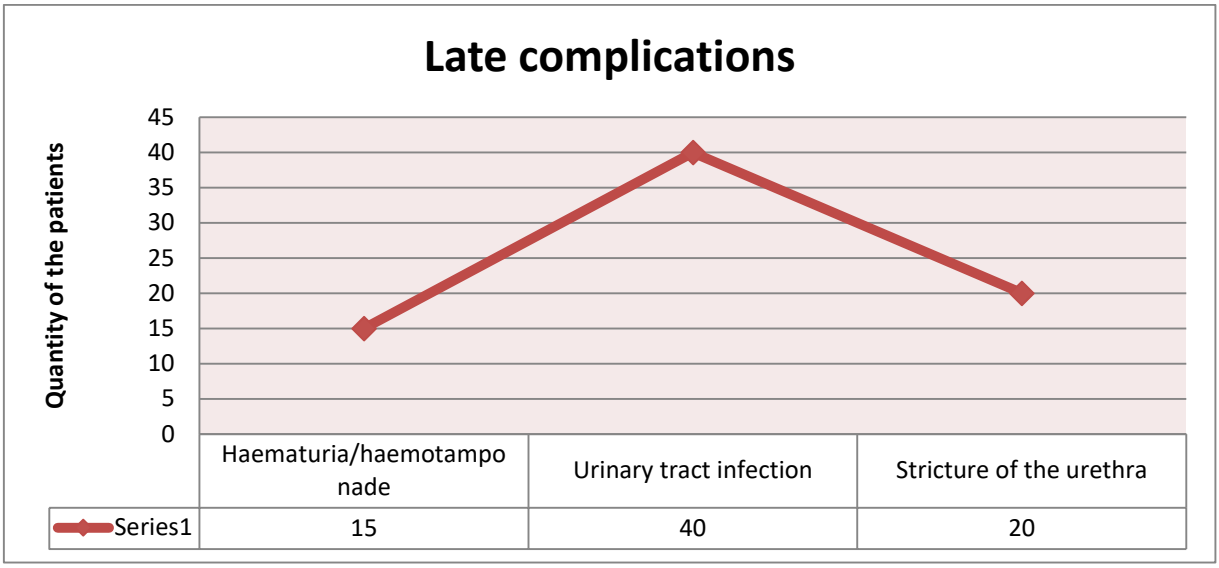


Figure 14. Late postoperative complications

On average, one in three operated had postoperative complications. No lethality and open reoperation were reported. The following complications were found and tabulated in different methods of transurethral surgery.

Hemotransfusion	2
Headache	3
Febrility	5
Nausea/vomiting	6
Haematuria/haemotamponade	7
Cardiovascular complications	3
Ileus	1
Lesion of the urethra	3
Lesion of the bladder	1
Lesion of the prostate	1
Reoperation	3
Urinary tract infection-early	1
Urinary tract infection-late	10
Stricture of the urethra	5

Table 18. Complications of monopolar resection

Only two patients required haemotransfusion within 24 hours due to haematuria and low baseline haemoglobin. Three patients required reoperation because of hemotamponade (Table 18).

Hemotonsfusion- intraoperative	2
Hemotransfusion	5
Headache	1
Febrility	1
Nausea/vomiting	2
Haematuria/haemotamponade	31
Pulmonary embolism	1
Lesion of the urethra	7
Lesion of the ureter	5
Lesion of the bladder	15
Lesion of the prostate	4
Urinary tract infection-early	3
Urinary tract infection-late	28
Stricture of the urethra	15

Table 19. Complications of bipolar resection

Two patients required hemotransfusion during surgery due to low baseline hemoglobin and exsanguinous hematuria with hematamponade. In 5 patients, isogroup blood was transfused within 24 hours of surgery. We did not have reoperation but several transurethral revisions in patients with hematotamponade (Table 19).

Headache	1
Lesion of the urethra	1
Lesion of the bladder	2
Urinary tract infection-late	2

Table 20. Complications after laser resection

Extraperitoneal rupture occurred in two patients, necessitating prolonged catheter wear (Table 20).

3. To study the clinical effectiveness of different methods of transurethral surgery on local tumor control

Patients were followed up at 3, 6, 9, 12 months in the first year and at 6 months in the second year.Laboratory analysis of full blood count, biochemistry,

haemostasis, electrolytes and common tumour marker (CEA) was performed in all patients. All patients were hospitalized and underwent ultrasonography of the POS and CT or MRI of the abdomen and small pelvis. Urethrocystoscopy was performed for diagnostic or therapeutic purposes in the presence of recurrence. The occurrence of recurrence correlated with the method of resection, tumor size, multifocality, degree of differentiation, comorbidity, and lifestyle.

Results were systematized and summarized by month of patients with local recurrence (Fig. 15). About 30% had early recurrence in the first 6 months.

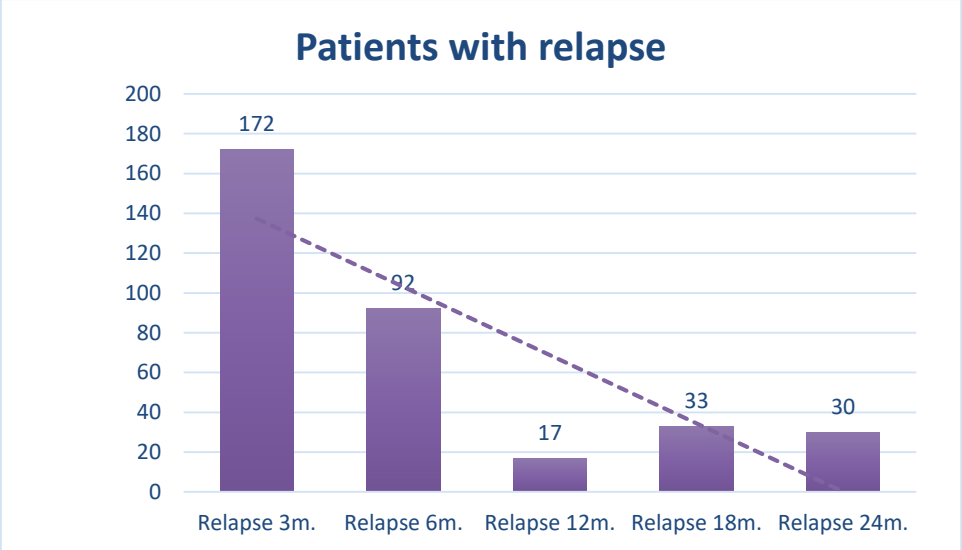


Figure 15. Distribution by month and occurrence of relapse

One-Sample Kolmogorov-Smirnov Test						
		Relapse 3m.	**Relapse 6m.**	**Relapse 12m.**	**Relapse 18m.**	**Relapse 24m.**
N		172	92	17	33	30
Normal Parameters	**Mean**	0.39	0.98	1	1	1
	Std. Deviation	0.49	0.15	0	0	0
Most Extreme Differences	**Absolute**	0.4	0.54	.	.	.
	Positive	0.4	0.44	.	.	.
	Negative	-0.28	-0.54	1.8E+308	1.8E+308	1.8E+308
Kolmogorov-Smirnov Z		8.39	5.21	-Infinit	-Infinit	-Infinit
Asymp. Sig. (2-tailed)		0	0	1	1	1

Table 21. Non-parametric analysis of relapse occurrence

The standard deviation at the 3rd month for relapse occurrence was 0.49, at the 6th month 0.15. At the end of the period it was practically 0 (Table 21).

3.1.Clinical effectiveness study in monopolar resection

Monopolar resection was performed in 102 patients (83 men and 19 women). At 3, 6, 12, 18 and 24 month, patients were hospitalized for control cystoscopy. They were categorized according to sex and occurrence of local recurrence (Fig. 16).

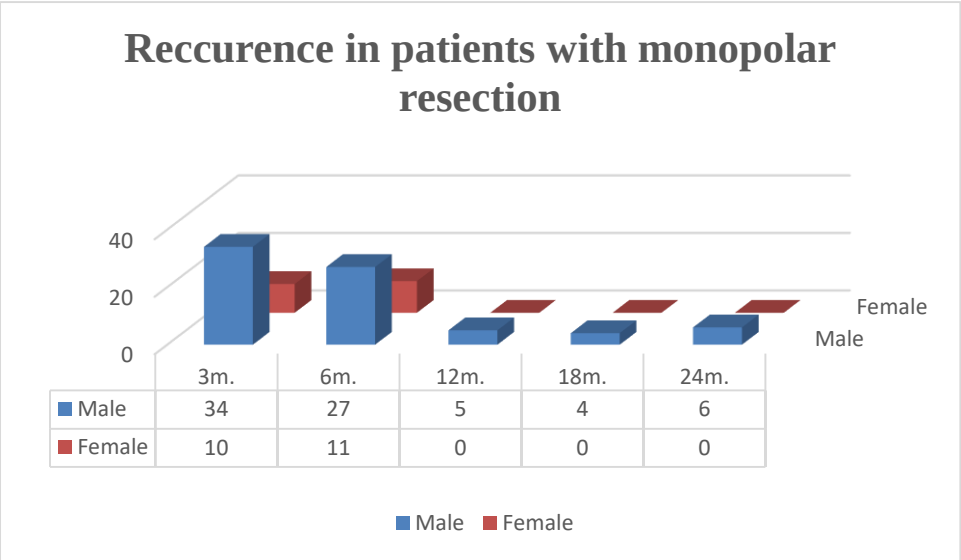


Figure 16. Recurrence in patients with monopolar resection

All patients were operated transurethrally using monopolar current. The re-hospitalization time was 2 to 4 days. The complications and side effects of the reoperation were not reported. A full course of intravesical chemotherapy or immunotherapy was performed after surgery.

3.2. Clinical effectiveness study in bipolar resection

Bipolar resection was performed on 319 patients(241 men and 78 women). At 3, 6, 12, 18 and 24 month patients were hospitalized for control cystoscopy. They were categorized by sex and occurrence of local recurrence (Fig. 17).

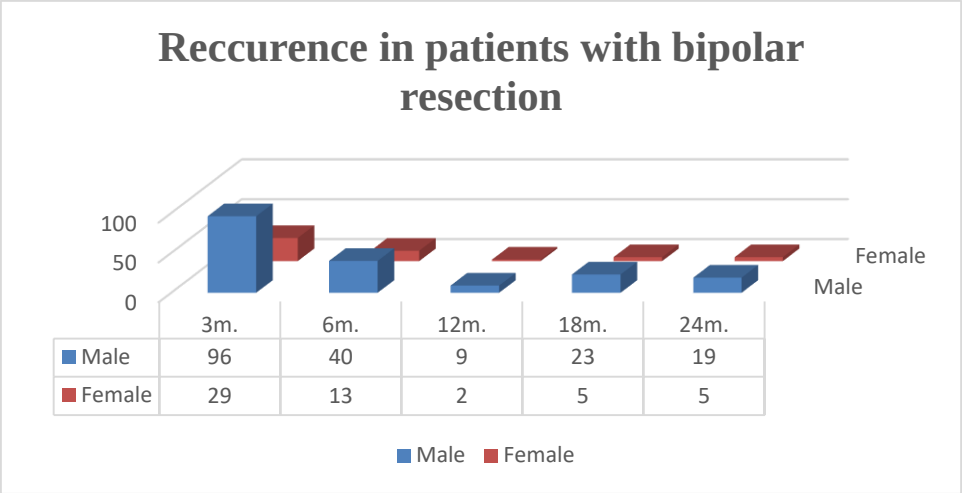


Figure 17. Recurrence in patients with bipolar resection

All patients were operated transurethrally using bipolar current. The re-hospitalization time was 2 to 4 days. The complications and side effects of the reoperation were not reported. A full course of intravesical chemotherapy or immunotherapy was performed after surgery.

3.3. Clinical effectiveness study in laser resection

23 patients (18 men and 5 women) were operated with laser resection. At 3, 6, 12, 18, and 24 month patients were hospitalized for control cystoscopy. They were categorized by sex and occurrence of local recurrence (Fig. 18).

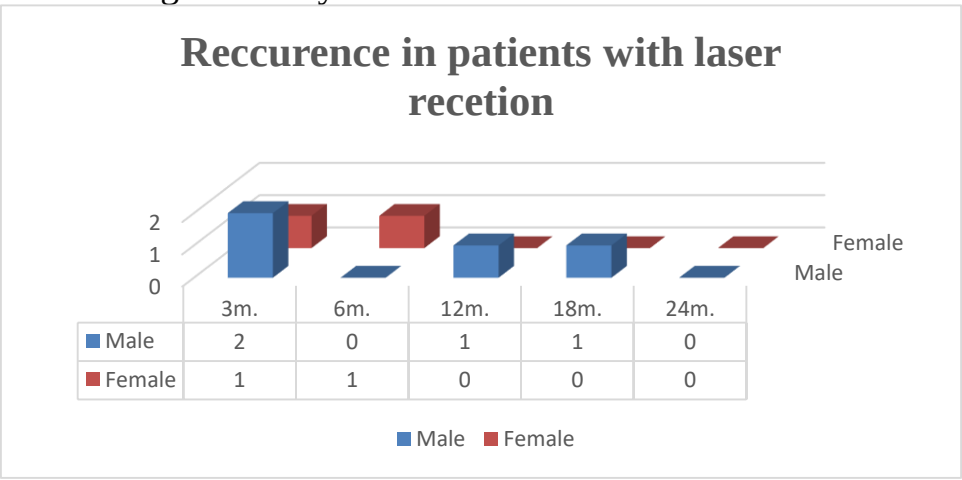


Chart 18. Recurrence in patients with laser resection

All patients were operated on transurethrally using a laser. The re-hospitalization time was 2 days. The complications and side effects of the

reoperation were not reported. A full course of intravesical chemotherapy or immunotherapy was performed after surgery.

Local recurrence with single or multiple lesions of varying degrees of differentiation was reported with all methods of transurethral surgery. All three treatments showed the occurrence of tumor recurrence regardless of the type of resection (Table 22).

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Monopolar resection × Reccurence 3m.	102	23.0%	342	77.0%	444	100.0%
Monopolar resection × Reccurence 6m.	40	9.0%	404	91.0%	444	100.0%
Monopolar resection × Reccurence 12m.	5	1.1%	439	98.9%	444	100.0%
Monopolar resection × Reccurence 18m.	5	1.1%	439	98.9%	444	100.0%
Monopolar resection × Reccurence 24m.	5	1.1%	439	98.9%	444	100.0%
Bipolar resection × Reccurence 3m.	319	71.8%	125	28.2%	444	100.0%
Bipolar resection × Reccurence 6m.	54	12.2%	390	87.8%	444	100.0%
Bipolar resection × Reccurence 12m.	11	2.5%	433	97.5%	444	100.0%
Bipolar resection × Reccurence 18m.	27	6.1%	417	93.9%	444	100.0%
Bipolar resection × Reccurence 24m.	25	5.6%	419	94.4%	444	100.0%
Laser resection × Reccurence 3m.	22	5.0%	422	95.0%	444	100.0%
Laser resection × Reccurence 6m.	1	.2%	443	99.8%	444	100.0%
Laser resection × Reccurence 12m.	1	.2%	443	99.8%	444	100.0%
Laser resection. × Reccurence 18m.	1	.2%	443	99.8%	444	100.0%

Laser resection × Reccurence 24m.	0	.0%	444	100.0%	444	100.0%

Table 22. Distribution by type of surgery and recurrence occurrence

4. To study the pharmacodynamics and pharmacokinetics of different chemotherapeutics and topical immunotherapeutics in patients with superficial urothelial carcinoma of the bladder

Leading guidelines for the treatment of superficial bladder cancer strictly recommend the use of chemotherapeutic and immunotherapeutic agents to treat and prevent late recurrence and progression of the disease. We divided the patients into four groups. Group A - no intravesical therapy. Group B- with administration of Mitomycin 40mg. Group C- with administration of Epirubicin 50mg. Group D- with administration of BCG (Fig. 19).

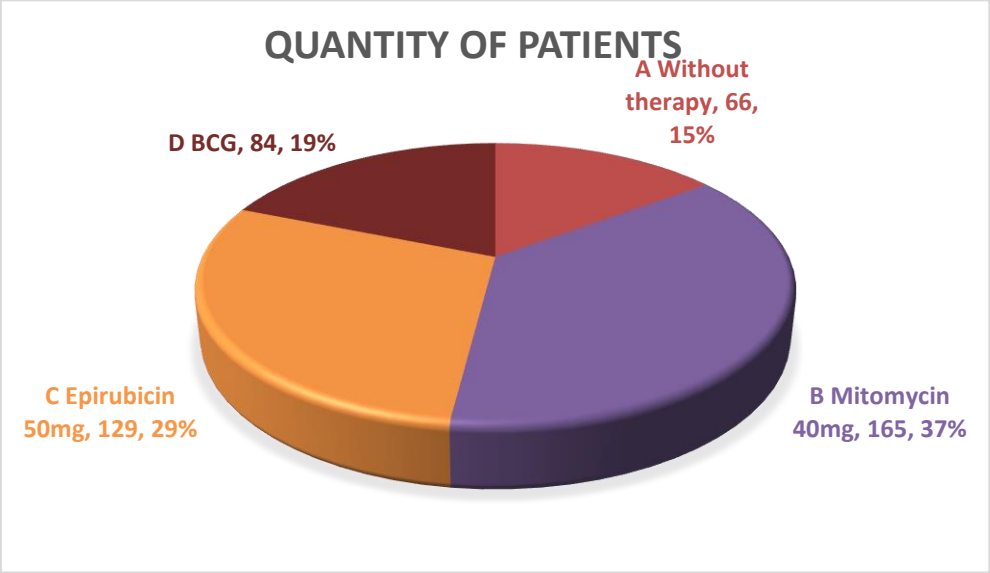


Figure 19. Distribution by groups with and without intravesical therapy

The criteria for administration of the different drugs was according to the patient's age, comorbidity, degree of malignancy and multifocality. Patients gave written informed consent for the procedure. The administration of intravesical therapy after surgical treatment significantly reduced the risk of disease recurrence and progression. Intravesical therapy was administered to 378 patients after primary resection according to a regimen (Table 23).

	Weekly	Monthly
Mitomycin 40mg.	6 weeks	6-8 months
Epirubicin 50mg.	6 weeks	6-8 months
BCG 4 amp..	6 weeks	6-12 months

Table 23. Treatment scheme

On (Fig. 20) it is noted that out of 66 patients without follow-up treatment 61 had early relapse at the 3rd month. This indicates that the administration of intravesical therapy after surgical treatment significantly reduces the risk of new recurrence. In all of these patients, intravesical treatment had to be administered after consecutive resection. There was a significant reduction in patients with recurrence after the first year.

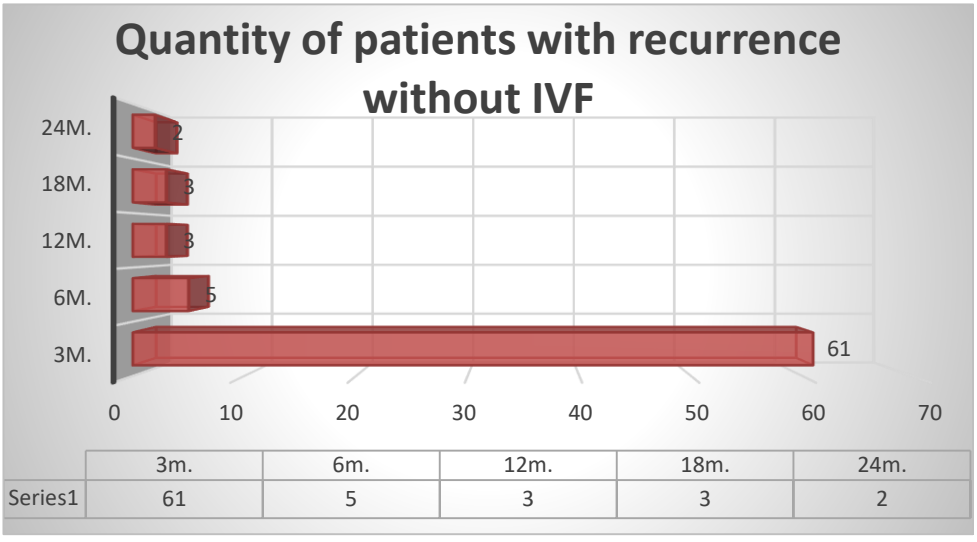


Figure 20. Quantity of patients with recurrence without IVF

In (Table 24) we can see the correlation between the different criteria. It is noted that the administration of Epirubicin is more frequent in patients with highly differentiated carcinoma. Moderately and low differentiated carcinoma required more frequent use of Mitomycin and BCG.

		SEX	AGE	G1	G2	G3	Multifocality	Mitomycin	Epirubicin	BCG

		SEX	AGE	G1	G2	G3	Multifocality	Mitomycin	Epirubicin	BCG
SEX	**Pearson Correlation**	1,00	,02	NaN	NaN	NaN	NaN	,01	,03	-,03
	Sig. (2-tailed)		,703	NaN	NaN	NaN	NaN	,799	,542	,509
	N	444	444	226	181	37	209	444	441	444
AGE	**Pearson Correlation**	,02	1,00	NaN	NaN	NaN	NaN	,01	-,07	-,01
	Sig. (2-tailed)	,703		NaN	NaN	NaN	NaN	,893	,170	,879
	N	444	444	226	181	37	209	444	441	444
G1	**Pearson Correlation**	NaN	NaN	NaN	NaN	NaN	NaN	-Infinity	-Infinity	+Infinity
	Sig. (2-tailed)	NaN	NaN		NaN	NaN	NaN	,000	,000	,000
	N	226	226	226	0	0	95	226	225	226
G2	**Pearson Correlation**	NaN	NaN	NaN	NaN	NaN	NaN	+Infinity	+Infinity	+Infinity
	Sig. (2-tailed)	NaN	NaN	NaN		NaN	NaN	,000	,000	,000
	N	181	181	0	181	0	91	181	179	181
G3	**Pearson Correlation**	NaN	NaN	NaN	NaN	NaN	NaN	-Infinity	-Infinity	-Infinity
	Sig. (2-tailed)	NaN	NaN	NaN	NaN		NaN	,000	,000	,000
	N	37	37	0	0	37	23	37	37	37
Multifocality	**Pearson Correlation**	NaN	NaN	NaN	NaN	NaN	NaN	-Infinity	-Infinity	-Infinity
	Sig. (2-tailed)	NaN	NaN	NaN	NaN	NaN		,000	,000	,000
	N	209	209	95	91	23	209	209	209	209
Mitomycin	**Pearson Correlation**	,01	,01	-Infinity	+Infinity	-Infinity	-Infinity	1,00	-,49	-,31
	Sig. (2-tailed)	,799	,893	,000	,000	,000	,000		,000	,000
	N	444	444	226	181	37	209	444	441	444
Epirubicin	**Pearson Correlation**	,03	-,07	-Infinity	+Infinity	-Infinity	-Infinity	-,49	1,00	-,29
	Sig. (2-tailed)	,542	,170	,000	,000	,000	,000	,000		,000
	N	441	441	225	179	37	209	441	441	441
BCG	**Pearson Correlation**	-,03	-,01	+Infinity	+Infinity	-Infinity	-Infinity	-,31	-,29	1,00
	Sig. (2-tailed)	,509	,879	,000	,000	,000	,000	,000	,000	
	N	444	444	226	181	37	209	444	441	444

Table 24. Correlation analysis in intralesional therapy

In (Fig. 21), it is seen that the local recurrence rate is highest at the 3rd postoperative month. It was reported that the occurrence of new tumor was correlated with patient's age, comorbidity, degree of differentiation and

smoking. All three therapies showed a significant reduction in local recurrence by the first year and a gradual increase in the second year.

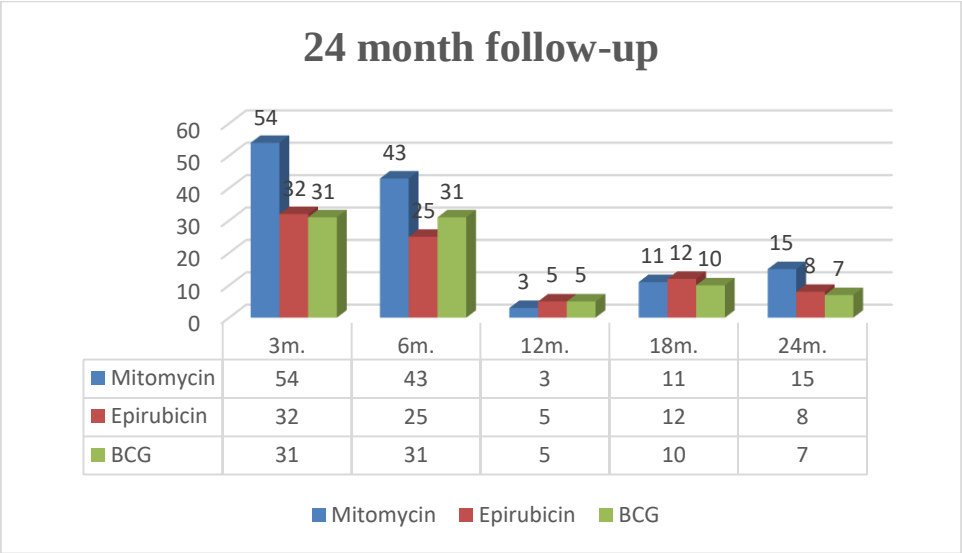


Figure 21. Presence of recurrence after intravesical therapy

The administration of the three types of therapeutics resulted in several side effects and complications, which were graphically presented (Fig. 22)

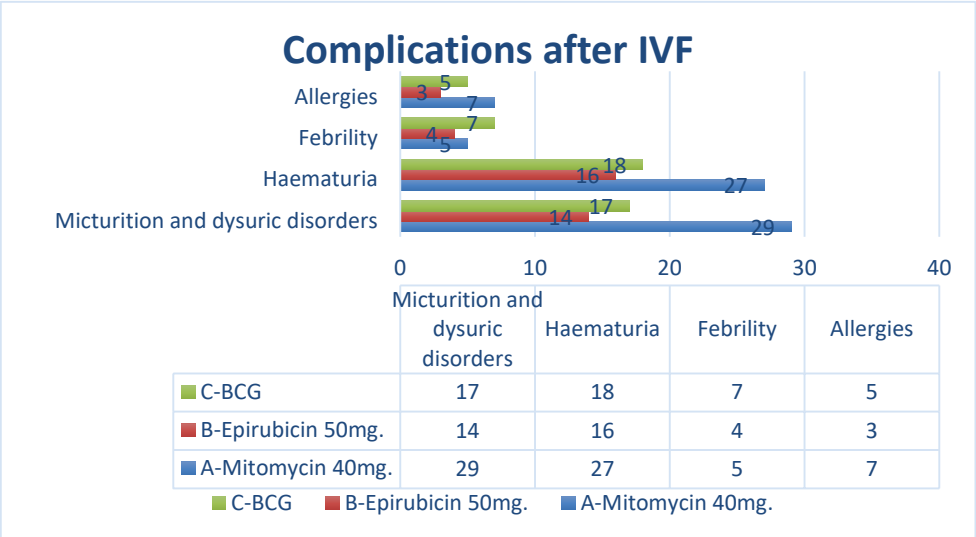


Figure 22. Complications after intravesical therapy

In all patients, treatment had to be temporarily stopped. Micturition and dysuric disorders were managed symptomatically, with 5 patients requiring catheterization. Haematuria also responded symptomatically, but in 22 patients a uretheral catheter was placed on irrigation. Febrility responded to analgesics,

and AB were included to the therapy of 7 patients. Allergic reaction developed as a general and local response which necessitated the use of high dose methylprednisolone and antihistamine derivatives. Patients who showed allergy discontinued the use of the allergenic agent and switched to other therapy.

5. To study the impact and side effects of local radiotherapy in patients with superficial bladder cancer

Frequently recurrent high- and moderate-risk urinary bladder tumors can be treated with highly focused radiotherapy.In patients with G2,G3,multifocality,frequent recurrence and progression, contemporary treatment is complemented by the use of a linear accelerator for radiotherapy. The bladder has good tolerance to radiotherapy.

The goal of radiation is to remove the tumor while preserving the structure and function of the surrounding normal tissues.

For this purpose, we used an Elekta linear accelerator for photon emission-guided radiosurgery. The absorbed daily dose was 1.8 Gy up to a total absorbed dose of 50-60 Gy. Eighteen patients who underwent bipolar elentroresection with 5 or more recurrences were included. Several courses of intravesical therapy were performed to all patients. Patients were divided into three groups (Fig. 23)

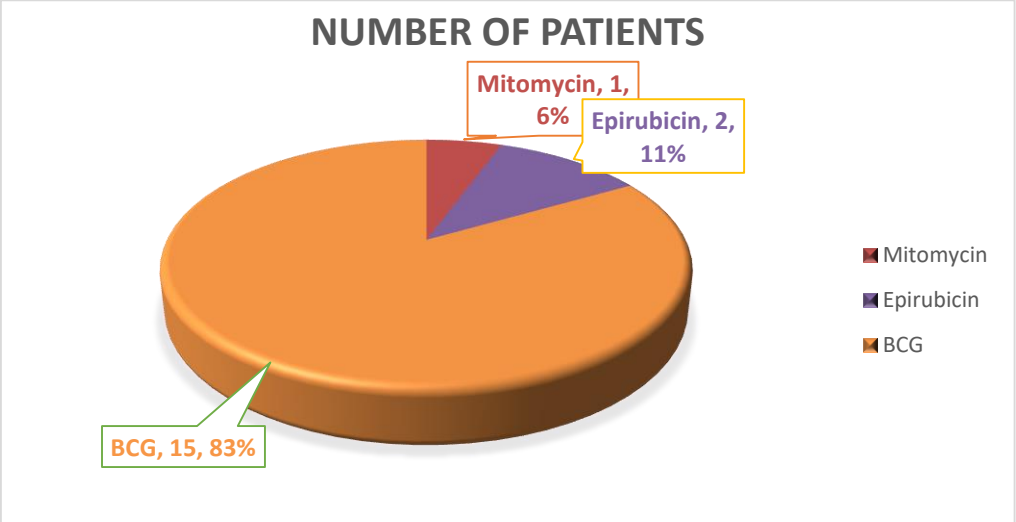


Figure 23. Number of patients for radiotherapy

The group of patients treated with BCG and G3 was the lead in the design of the radiosurgery algorithm. All patients lacked previous courses of radiotherapy. Dose and duration was determined by nomogram for the respective linear

accelerator type. The approach was individualized and all radiation protection rules were followed. The first dose of ionizing energy took place 30-40 days after the last course of intravesical therapy. After the complete course of radiotherapy, local recurrence was found in 3 patients with solitary lesions (Fig. 24). This shows a 4-fold reduction in new lesion appearance in patients undergoing radiosurgery.

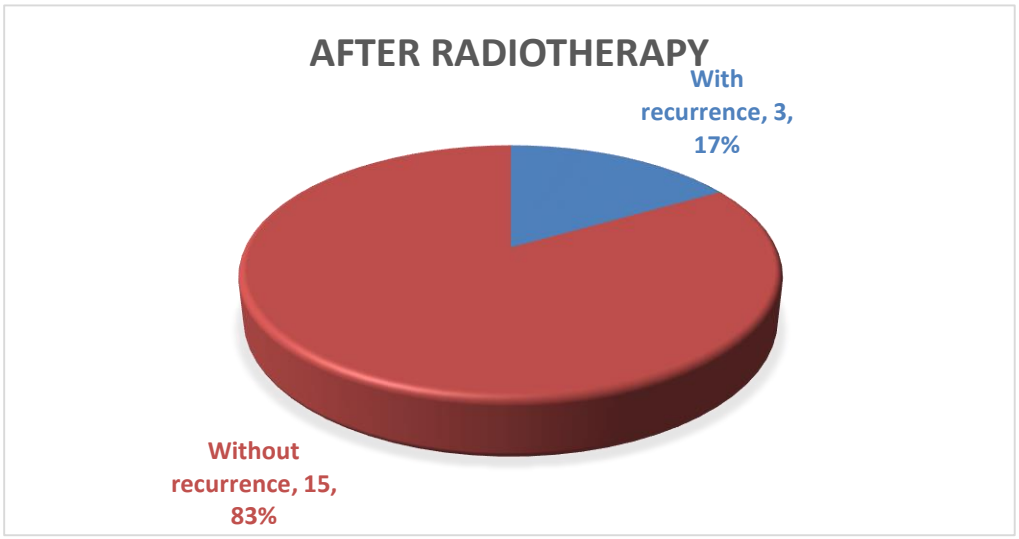


Figure 24. Distribution of patients after radiotherapy

Radiation therapy is an effective treatment for patients with bladder cancer. It provides long-term disease control with preservation of normal bladder function.

After radiotherapy, several side effects of ionizing energy were found.

The development of radicin cystitis is presented by symptoms (Fig. 25).

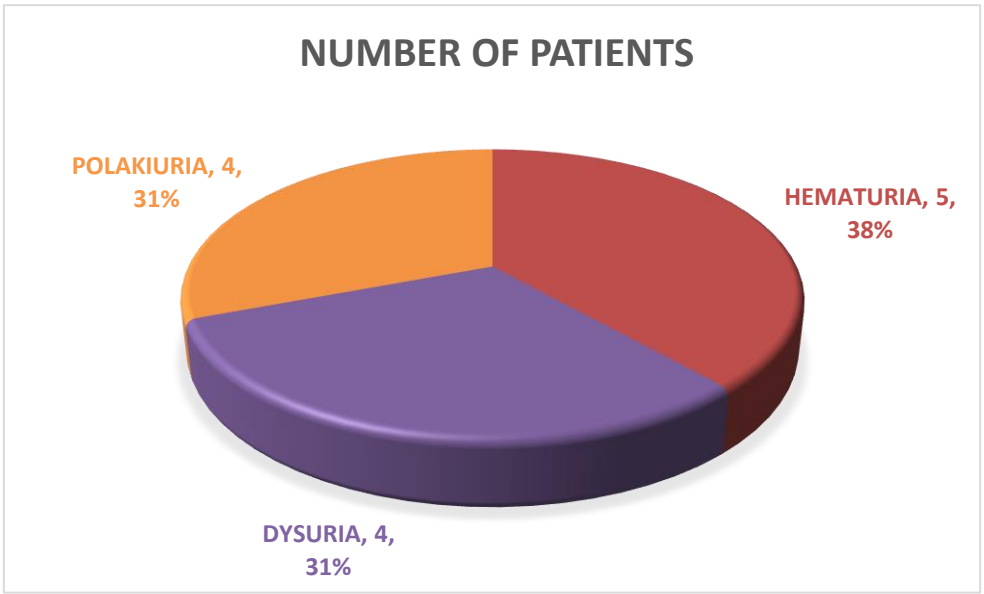


Figure 25. Symptoms in radiation cystitis

Haematuria was leading but persisted up to a week. Dysuria and pollakiuria persisted up to 1 month. For the treatment of radiation cystitis, we used symptomatic agents (analgesics and nonsteroidal anti-inflammatory drugs) and topical sodium hyaluronate. We used for intravesical application 40mg. 50ml. Cystistat for 4 weeks in 10 patients and for 8 weeks in 3 patients. Data and results were summarized at the 3rd month. Diagnostic cystoscopy was performed in all patients before starting treatment and at the third month. All had uroculture without bacterial growth and no laboratory evidence of inflammation.

Mucosal hyperemia with glomerulations was found in 10 patients (Fig. 16).

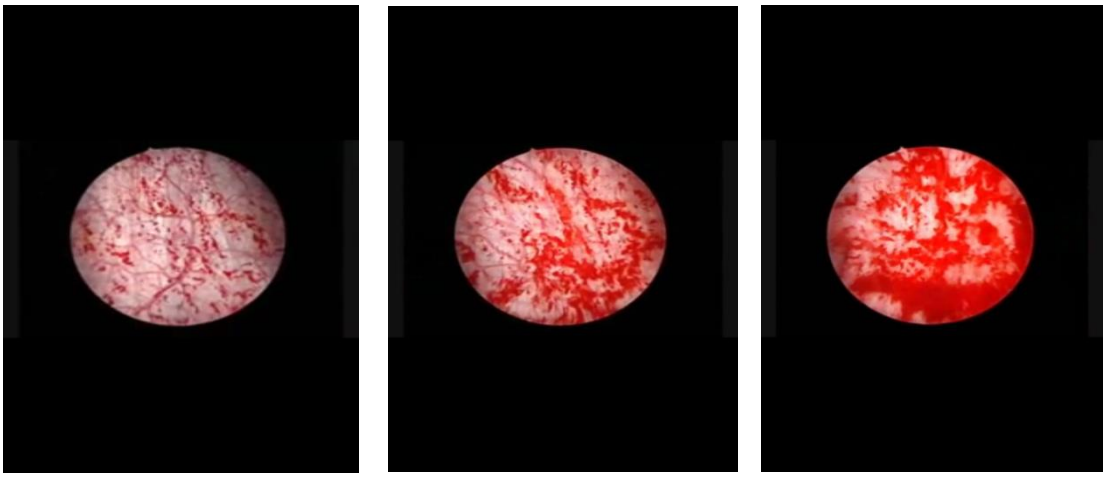


Figure 16. Types of glomerulations after radiotherapy

Erosions were found in 3 patients (Fig. 17).

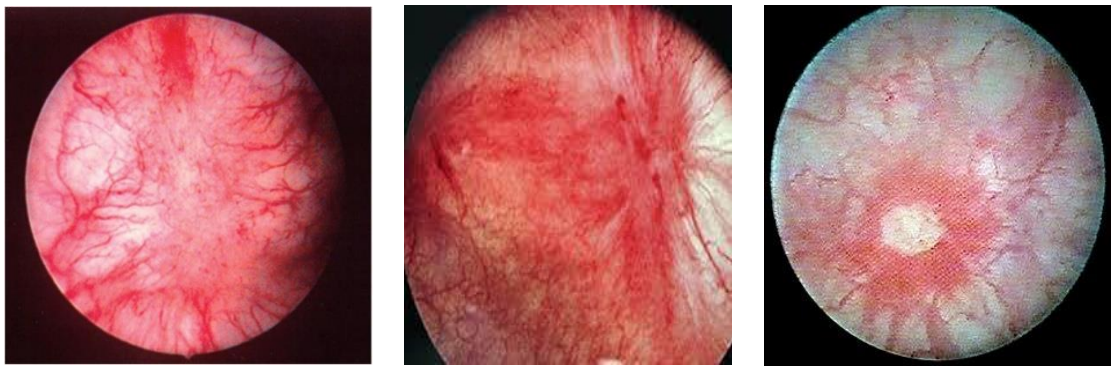


Figure 17. Hunner erosions

In 13 patients with radiation cystitis who received once-weekly intravesical hyaluronic acid for 4 weeks, there was a mean reduction in symptoms, i.e., nicturia and pain, by 40% and 30%, respectively, and reduced analgesic use by 41% (Fig. 26).

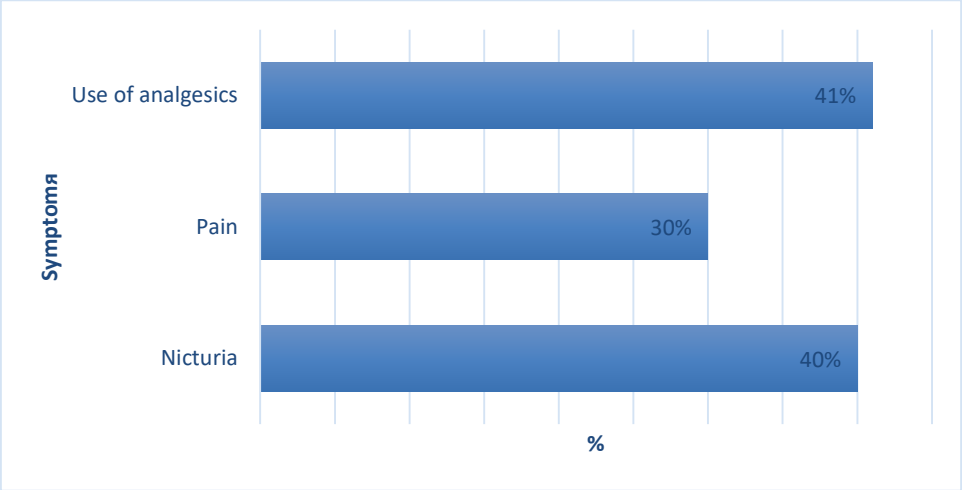


Figure 26. Regression of symptoms after sodium hyaluronate

At the cystoscopy performed at 3 months, the following was found. Only 3 patients were found to have hyperemia with glomerulations without micturition and dysuric complaints (Table 25).

Treatment course	Normal mucosa	Hyperemia	Erosion
4 weeks	8 (58,1%)	2(19,3%)	0(0%)
8 weeks	2(16,1%)	1(6,5%)	0(0%)

Table 25. Cystoscopy results after local therapy

6. To investigate the impact of comorbidity, diet and smoking on the occurrence of primary and recurrent superficial bladder cancer

Smoking, comorbidity, diet and intake of various medications play a pivotal role in the occurrence, recurrence and progression of urothelial carcinoma of the bladder. Changing these etiological factors in a large percentage can reduce the

incidence of patients with this disease. Smoking cessation, healthy diet and lifestyle modification were recommended in all patients.

We monitored the recurrence rate in 380 patients with comorbidity (CVS, RS, metabolic diseases) and 98 patients (active smokers).

Data on patients with relapse occurrence over a 24-month period in both groups were summarized and presented in graphical form (Figs. 27, 28)

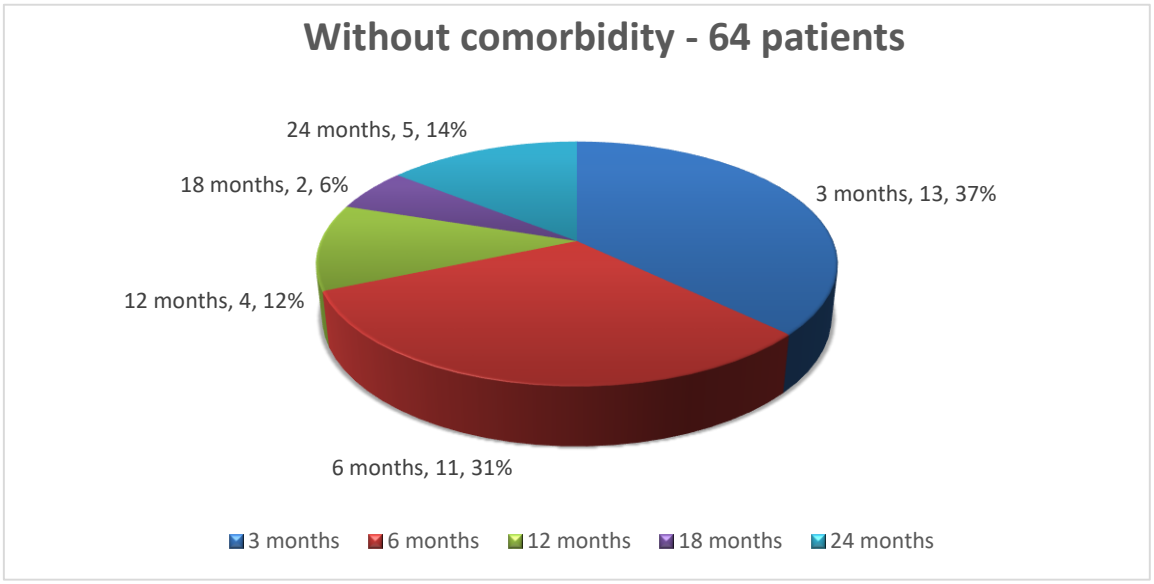


Figure 27. Patients with relapse without concomitant diseases

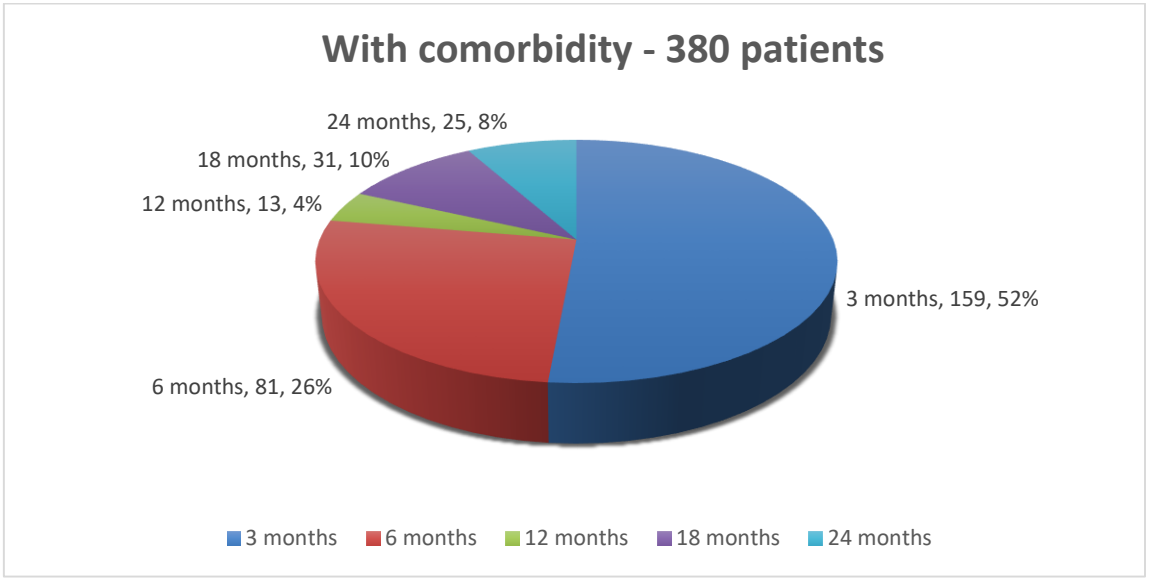


Figure 28. Patients with relapse with concomitant diseases

It is noted that patients without comorbidities have a lower risk of new recurrence by the 3rd month. Thereafter, the rate of newly fused tumor is marginally higher in comorbid patients (Fig. 29).

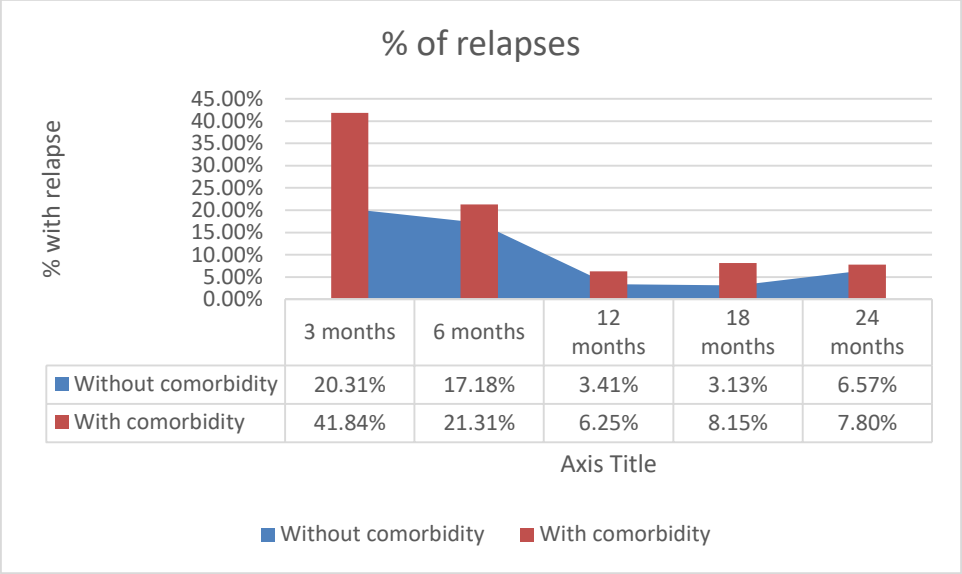


Figure 29. Rate of new relapse over a 24-month period

The nonparametric analysis revealed that the occurrence of a new tumor was directly associated in patients with comorbidity (Table 26).

One-Sample Kolmogorov-Smirnov Test							
		comorbidity	Relapse 3m.	Relapse 6m.	Relapse 12m..	Relapse 18m.	Relapse 24m.
N		444	443	94	17	33	30
Normal Parameters	Mean	.86	.39	.98	1.00	1.00	1.00
	Std. Deviation	.35	.49	.15	.00	.00	.00
Most Extreme Differences	Absolute	.51	.40	.54	.	.	.
	Positive	.34	.40	.44	.	.	.
	Negative	-.51	-.28	-.54	1.8E+308	1.8E+308	1.8E+308
Kolmogorov-Smirnov Z		10.85	8.39	5.21	-Infinit	-Infinit	-Infinit
Asymp. Sig. (2-tailed)		.000	.000	.000	1.000	1.000	1.000

Table 26. Non-parametric analysis for comorbidity and relapse association

In 98 active smokers, daily cigarette intake was discontinued or reduced. Relapse was reported at 3, 6, 12, 18, and 24 month. The results were presented in graphical form (Fig. 30). In 30% of those who restricted smoking, relapse was found to occur at the 3rd month (Table 27).

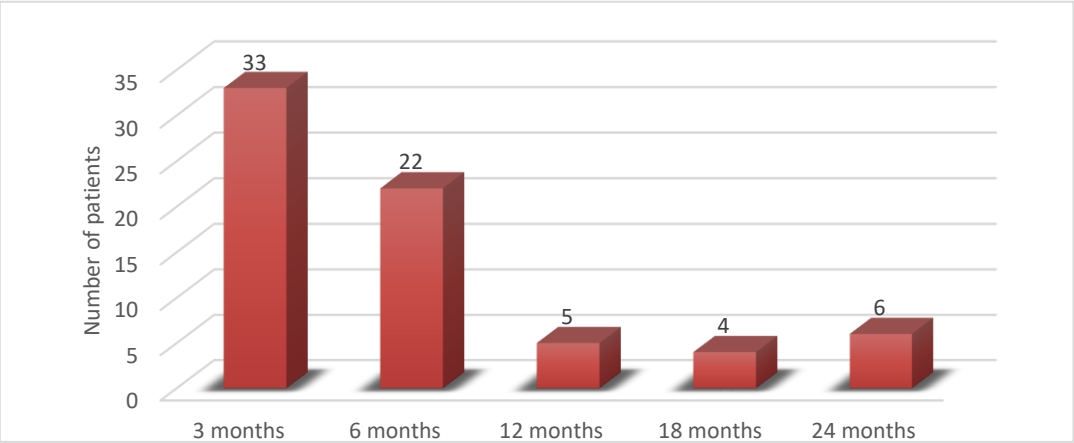


Figure 30. Number of patients with relapse in 24 mo.

		Active smokers	Relapse 3m.	Relapse 6m.	Relapse 12m.	Relapse 18m.	Relapse 24m.
Active smokers	Pearson Correlation	1.000	-.045	.083	NaN	NaN	NaN
	Sig. (2-tailed)		.348	.432	NaN	NaN	NaN
	N	442	441	93	17	33	30
Relapse 3m.	Pearson Correlation	-.045	1.000	-.045	NaN	NaN	NaN
	Sig. (2-tailed)	.348		.665	NaN	NaN	NaN
	N	441	443	93	17	33	30
Relapse 6m.	Pearson Correlation	.083	-.045	1.000	NaN	NaN	NaN
	Sig. (2-tailed)	.432	.665		NaN	NaN	NaN
	N	93	93	94	16	8	8
Relapse 12m.	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN	NaN		NaN	NaN
	N	17	17	16	17	5	4
Relapse 18m.	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN	NaN	NaN		NaN
	N	33	33	8	5	33	13
Relapse 24m.	Pearson Correlation	NaN	NaN	NaN	NaN	NaN	NaN
	Sig. (2-tailed)	NaN	NaN	NaN	NaN	NaN	
	N	30	30	8	4	13	30

Table 27. Correlation analysis smoking - relapse occurrence

7. To develop a multimodal algorithm for the diagnosis, treatment and follow-up of patients with overlying bladder cancer

The most common symptom of bladder cancer is painless haematuria. Symptoms related to urination may suggest Tis. There is no specific screening to detect bladder carcinoma. Imaging studies and direct visualization with a cystoscope make an accurate diagnosis. We present an algorithm for the diagnosis and treatment of NMIBC (Table 28).

Symptoms	Diagnosis	Treatment
Haematuria and/or blood clots in urine Dysuria Polyuria Urgency	Physical examination	**Low-risk tumors** TURB. Immediate intravesical chemotherapy Mitomycin 40 mg. Epirubicin 50mg.
Suprapubic pain Abdominal pain Low back pain	Laboratory examinations Tumor markers	**Moderate-risk tumors** TURB. Immediate intravesical chemotherapy Mitomycin 40 mg. Epirubicin 50mg. BCG
Fatigue Loss of appetite or weight loss	Imaging studies Ultrasound, CT, MRI, PET-CT Cystoscopy Transurethral resection	**High-risk tumors** TURB. Immediate intravesical chemotherapy Mitomycin 40 mg. Epirubicin 50mg. BCG Radiotherapy Immunotherapy

Table 28. NMIBC algorithm

The follow-up of bladder cancer depends on the type and degree of risk for the disease. In low-risk muscle-invasive disease, progression is rarely seen beyond the fifth year, and invasive surveillance methods can then be substituted for noninvasive ones.

So far, there is no reliable noninvasive method of bladder cancer follow-up that can replace cystoscopy. It is the main diagnostic method for monitoring the condition.

In patients with high-risk superficial urothelial carcinoma, follow-up should continue for the rest of their life because the disease recurs even after 10 years.

Follow-up of low- and moderate-risk patients requires cystoscopic examination at 3, 9 and 18 month and once a year thereafter.

Follow-up of high-risk patients requires cystoscopic examination

* every 3 months for the first 2 years

* every 6 months for the next 2 years

* once a year thereafter

We suggest the following schedule for follow-up of patients with bladder cancer (Table 29).

Examinations	**Period of follow-up examinations**
History and physical examination	3 months
Ultrasonography of abdominal organs	3 months
Chest radiography	6 months
Consultation with urologist	3 months
Cystoscopy	3 months
Cytology/bladder biopsy	3 months
Cytology of urine	6 months
CT scan of chest, abdomen, pelvis	If necessary
Bone scintigraphy	If necessary
MRI, PET-CT	If necessary
Blood count	3 months
ASAT, ALAT	3 months
Serum urea, creatinine	3 months
Serum total protein.CEA	6 months

Table 29. Follow-up of patients with NMIMC

V. Discussion

Discussion of Task 1.

Looking at the studies reported in the literature, it is clear that most centers in Europe and Bulgaria working on a multimodal approach to the treatment of superficial bladder cancer follow similar criteria for patient selection. The inclusion criteria for the studies are age over 18 years, histologically proven carcinoma. Individual groups such as tumor localization, degree of differentiation, tumor size, multifocality and patients with comorbidity and

smoking cessation overlapped in other studies. Selection for the multidisciplinary approach was prepared by a team of specialists in urology, medical oncology, pathology, radiology, imaging, internal medicine, and medical physicists. In creating this algorithm, the aim was to follow patients and correlate the criteria with the occurrence of relapse and/or disease progression. The exclusion criteria were adopted so that there would be no large differences in the clinical and laboratory status of the patients and this would lead to incomparable conclusions and results.

Discussion of Task 2.

To study the safety and security of transurethral surgery, we divided the patients into three groups. Group A- patients with monopolar resection- 102 (men 83: women 19). Group B- patients with bipolar resection- 319 (men 241: women 78). Group C- patients with laser resection-23 (males 18: females 5). Clinical data , including preoperative, operative and postoperative follow-up of the groups were recorded and summarized. In all three groups, patients were selected according to criteria- age, tumor size and localization, multifocality, and degree of differentiation. The groups were statistically equated on the known confounding factor of age, which means that the necessary prerequisite for their correct comparison with respect to different methods of transurethral surgery was met. The mean age in group A was - males 66.5y and females 71.5y. In group B it was - men 68years and women 67years. In group C it was - men 59,4y and women 63,4y. There was no significant statistical difference of age in the three groups. Patient demographics and tumor characteristics in the three groups were compared before surgery. There was no comparative difference in the results of surgery between the groups. In the monopolar resection group, the mean operation time was 29.43 min and the mean hospital stay was 2.52 days. In the bipolar resection group, the mean operative time was 26.88 min and the mean hospital stay was 2.44 days. In the laser resection

group, the mean operative time was 25.17 min and the mean hospital stay was 2 days. According to (Del Rosso A, Pace G 2013) the mean operative time was 27 minutes for bipolar plasmakinetic transurethral bladder resection and 31 minutes for monopolar transurethral bladder resection. In another study (Zhao C, Tang K, Yang H 2015), bTURB was associated with shorter operative time (P = 0.002) and shorter hospital stay (P < 0.001) compared with mTURB. Using laser energy, according to (Xu J. Wang C. Ouyang J. Sun J 2020), the analysis showed no significant difference in operation time and mean hospital stay (mean difference = -0.2; 95% , days from 1.89 to 2.29; p = 0.85). According to our study, there was no significant difference in time and hospital stay in the three groups. This overlaps with many other studies. Intraoperative and postoperative complications occurred in all three transurethral resection groups. Of the entire population of 444 patients, 7 required haemotransfusion within 24 hours due to significant bleeding in excess of 500 ml. In 3 patients, blood transfusion took place after the end of surgery and the rest within 24 hours. We had 18 bladder lesions with extraperitoneal localization due to n. obturatorius excitation. We found 10 lesions of urethra, 5 lesions of ureter and 5 lesions of prostate. All ureteral lesions were prosthetized with JJ endoprosthesis. Complications on the ureter and prostate side required prolonged catheter wear for up to 7 days. Headache, nausea and vomiting corresponded with hypertensive crisis, anesthetic action and psycho-emotional instability. In 2 patients with monopolar resection, hemotransfusion was required in the first 24 hours. In 5 patients with bipolar resection, blood transfusion was performed within 24 h. There was no significant bleeding or hemotransfusion in those operated with the holmium laser. Monopolar and bipolar resection revealed obturator syndrome in 31 patients. The mTURB:bTURB ratio was 6:25 patients. Despite the higher number in bipolar resection, the ratio in both groups was statistically insignificant with p= 0.005. According to (Rabee Abdallah Yassein, Ayman Mohtady Edrees 2020) intraoperatively there was a significant difference

between the two groups in terms of obturator reflex which was higher in the M-polar TURB group than the B-polar TURB group (25% vs 5%; P= 0.013) respectively. The operative time was shorter in the B-polar TURB group than the M-polar TURB group, but with no statistically significant difference. In (Chenming Zhao, Kun Tang, Huan Yang 2016), bTURB was associated with shorter operative time (P = 0.002), shorter hospital stay (P < 0.001), less established blood loss (P < 0.001), and shorter catheterization time (P = 0.004). There were fewer complications such as obturator nerve reflex (P < 0.001) and bladder perforation (P = 0.003) in the bTURB group. There was a lower relative proportion of intraoperative complications in bipolar resection compared with monopolar resection. Early and late postoperative complications were also reported and pooled. Early urinary tract infection was found in group A in 1 patient and group B in 3 patients. Late urinary tract infection was found in group A in 10 patients and group B in 28 patients. These results relative to the total of the two groups had no statistical difference. According to (K Xie, D Cao 2021) bTURB has no significant advantages in efficacy and safety in NMIBC treatment compared with that in mTURB. Thus, bTURBT cannot completely replace mTURBT as a safer and more effective treatment of NMIBC. In laser resection, we reported 1 urethral lesion and 2 bladder lesions intraoperatively. No hemotransfusion was required and we had no obturator syndrome.According to (Nischith D'souza and Ashish Verma 2016)the HoL-EBRBT group had fewer intraoperative and postoperative complications including obturator nerve reflex (P < 0.01), bladder perforation (P < 0.01), and bleeding (P < 0.01). There were no significant differences among the three groups in the occurrence of urethral strictures. Patients in the HoL-EBRBT group had shorter catheterization and hospitalization times than those in the mTURB and bTURB groups (P<0.01), and there were no significant differences in any risk subgroup. Our findings and conclusions are entirely consistent with the results of other studies.

Discussion of Task 3.

To investigate the clinical effectiveness of different methods of transurethral surgery on local tumor control we followed the patients at 3, 6, 12, 18 and 24 month. We found that the occurrence of recurrence correlated with surgical method, tumor size and multifocality, degree of differentiation, comorbidity, and lifestyle. According to our study, 172 patients had early recurrence at month 3. Of these, 61 were without subsequent intravesical therapy, which is more than 30%. Significant deviation at month 3 was 0.49, at month 6 was 0.15, and at month 12 was 0. That is, by the end of the first year, the number of patients with recurrent tumor decreased significantly. In the monopolar resection group, there were 44 patients with recurrence at month 3, 34 males and 10 females. At the 6th month there were 38 patients - 27 men and 11 women. There was a marginal decrease in patients for the first 6 months. For the bipolar resection group there were 125 patients with recurrence at month 3 - 96 men and 29 women. At month 6 there were 53 patients - 40 men and 13 women. The bipolar resection group showed an almost 50% reduction in local recurrence compared to the number at month 3. At 12th, 18th and 24th month the number of patients with mTURB were 5, 4 and 6 respectively, while in bTURB they were 11, 28 and 24. Relative to the total number in both groups, it can be seen that the number of patients with local recurrence was lower in bipolar resection. There were 2 male and 1 female recurrence in laser resection patients at month 3. By the 24th month, there were 3 more patients with recurrence. According to a study (Esmee IML Liem , Michael McCormack , Edie C Chan 2020) out of 716 patients 185(25.8%) developed recurrence (mTURB = 88, bTURB = 97). Recurrence-free survival at 12 months in the mTURB and bTURB groups was 70% and 74%, respectively (P = 0.410). According to Mao X, Zhou Z 2021, there was no significant difference in subepithelial and muscle tissue sampling (P = 0.43), recurrence-free survival at 6 months (P = 0.68) and 12 months (P = 0.78). In

another study by Xu J. , Wang C., Ouyang J. transurethral laser surgery for NMIBC compared with TURBT was associated with lower complication rates, lower recurrence rates, and faster postoperative recovery. According to authors Karim Chamie, Mark S. Litwin-2021 recurrence rates at 2, 5, and 10 years were 61.1%, 69.5%, and 74.3%, respectively. The corresponding annual progression rates were 12.8%, 22.8% and 33.3%. There are no definitive data to confirm or reject the advantages of the three types of transurethral surgery in terms of recurrence and disease progression. In patients with tumor size greater than 3 cm, multifocality, and high risk, the occurrence of recurrence did not correlate with the method. Based on these results, bTURB is as safe and effective as mTURB in the treatment of primary NMIBC. It appears that bTURB has no obvious advantages over mTURB in terms of operative time, perioperative and postoperative complication rates, and recurrence rates after 12 months.

Discussion of Task 4.

To study the pharmacodynamics and pharmacokinetics of topical chemotherapeutics and immunotherapeutics in the treatment of patients with superficial urothelial carcinoma, we established four groups. Group A-without intravesical therapy-66 people, group B-with administration of Mitomycin 40mg-165 people, group C-with administration of Epirubicin 50mg-129 people and group D-with administration of BCG-84 people. The dose administered was 6 weeks followed by 6 months to 1 year. Initially, 61 patients without IVT had local recurrences at month 3. Adjuvant chemotherapy was given after reoperation in all. At 6, 12, 18, and 24 months, 5, 3, 3, and 2 patients, respectively, relapsed. There was correlation between different medications , patient age, gender, degree of differentiation and multifocality. In low and moderate risk patients we used epirubicin and mitomycin while in high risk group we approximated mitomycin and BCG. All three therapies showed a significant reduction in local recurrence in the first year. In group B, 54 had

local relapse at 3 years, 43 at 6 years and 3 at 12 years in the first year. From group C- local recurrence had at 3m.- 32, at 6m.- 25, at 12m.- 5 people for the first year. From group D- local relapse they had at 3y.- 31, at 6y.- 31, at 12y.-5 people for the first year. According to Shang PF, Kwong J 2011, of the evaluable patients, 35.5% (195/549) in the BCG group and 51.4% (289/562) in the EPI group had tumor recurrence ($P<0.05$) in the first year. Kuroda et al randomized 622 patients with Ta-T1 G1-2 NMIBC to adjuvant treatment with 17 doses of epirubicin 20 mg/40 ml for 12 months, 12 doses of epirubicin 30 mg/40 ml for 7 months, or 9 doses of epirubicin 40 mg/40 ml for 4 months. At 2-year follow-up, the recurrence-free rates were 48.7%, 55.1%, and 60.1%, respectively, showing the greatest effect of the highest-dose regimen administered for a short period of time. We administered a dose of 50mg/25ml Epirubicin for 6 weeks followed by the same dose for 6 months. We reported 24 months recurrence-free survival of 55% and 61% for the first year and second year, respectively. Nomata et al treated 125 patients with Ta-T1 G1-2 NMIBC with 30mg/30ml epirubicin, either 19 times in 1 year or 12 times in 5 months with 48.5% and 55.1% of patients relapse free at 3-year follow-up, respectively, which is a nonsignificant difference. During the median follow-up period of 46.5 months in the immediate MMC group and 47.2 months in the MMC group, early relapse (within 1 year) occurred in 6 of 53 patients (11.3%) in the MMC group and in 18 of 62 patients (29.0%) in the MMC group ($p<0.02$), (Seok Jin Jung, Hyuk Soo Chang 2011). We administered a dose of 40mg/50ml Mitomycin for 6 weeks followed by the same dose for 6 months. We reported 24 months recurrence-free rates of 66% and 61% for the first year and second year, respectively. Intravesical immunotherapy results in a massive local immune response characterized by induced expression of cytokines in the urine and bladder wall and influx of granulocytes and mononuclear cells. BCG is an attenuated mycobacterium developed as a vaccine against tuberculosis. The vaccine is reconstituted with 50 ml of saline and must be administered via a

urethral catheter under gravity drainage soon afterwards as aggregation occurs (Ratliff et al 1994). The exact antitumor effect of BCG has not been elucidated to date, but several groups have demonstrated that increases in T helper cytokines (e.g., gamma, interleukin-2) after BCG instillations predict improved outcome (de Reijke et al . 1996 ; Ratliff et al . 1986 ; Haaff et al.1986). Four meta-analyses have confirmed that BCG after TUR is superior to TUR alone or TUR plus chemotherapy in preventing NMIBC recurrence in patients with Ta and T1 tumors (Shelley et al . 2001 ; Han et al . 2006) with high risk of tumor recurrence (Shelley et al . 2004) and intermediate or high-risk status (Böhle et al . 2003). Also, there are studies that confirm the superiority of BCG over the combination of epirubicin and interferon (Duchek et al. 2010), mitomycin C (Järvinen et al. 2009), or epirubicin (Sylvester et al. 2010) alone in preventing tumor recurrence, in moderate- and high-risk groups. Several adverse events and complications occurred during intravesical therapy, which were summarized and presented in tabular and graphical form. We reported the occurrence of allergy, febrility, hematuria, and the presence of micturition and dysuria disturbances. Allergy was found in 5 subjects with BCG, 3 with epirubicin and 7 with mitomycin. In all BCG patients, the allergic reaction was manifested by a local reaction- pruritus, genital hyperemia and hematuria with dysuria, and a general reaction- hypotension and urticaria on the trunk and extremities (Van de Meijden et al. 2003). Side effects can be divided into local (e.g. genital discomfort, haematuria) and systemic side effects (e.g. fever, hepatitis, pneumonitis, allergic reactions). Major complications may occur after systemic absorption of the drug. Thus, BCG should not be administered during the first 2 weeks after TURB in patients with macroscopic hematuria, symptomatic urinary tract infection, or after traumatic catheterization. BCG should not be used in immunocompromised patients (Lamm et al. 1992). The main side effects associated with BCG are increased urinary frequency (71%), cystitis (67%), hematuria (23%), and fever (25%), (Shelley et al. 2000). From our study, the

highest number of patients with febrility up to 38° was reported in the BCG-treated group- 7 souls, followed by those with epirubicin- 5 and mitomycin- 4. We managed the febrile state with antipyretics and analgesics without including antibiotic treatment. Haematuria and presence of micturition and dysuria was highest in the mitomycin group, 27 and 29 patients respectively. With epirubicin, the ratio was 16 and 14 patients. In those undergoing immunotherapy, 18 and 17 patients, respectively. Relative to the total number receiving adjuvant chemotherapy, it is noted that BCG patients had a higher rate of side effects. Cystitis was more common in the BCG group compared with the mitomycin group (53.8% vs. 39.2%, $p < 0.001$). Local and systemic toxicities were more common in the BCG group, except for allergy and skin reactions, which were more common in the mitomycin group (Bohle et al. 2003).

Discussion of Task 5.

To study the impact and side effects of local radiotherapy in the treatment of patients with superficial urothelial carcinoma, we established three working groups. Criteria such as frequently recurrent tumors, high-risk patients, multifocality, and refusal of radical cystectomy were guiding our study. Of the 18 patients we included, 15 had had several complete courses of BCG, 2 with epirubicin and 1 with mitomycin. All patients had more than 5 recurrences in 24 months who, because of worsening general condition or because of refusal of radical treatment, underwent a course of radiotherapy. The European Committee on Radiotherapy has developed evidence-based guidelines for the use of radiotherapy in the treatment of patients with bladder cancer. The strength of evidence supporting each recommendation was graded on a 4-point scale (M Milosevic, M Gospodarowicz , A Zietman , F Abbas 2007). Radiotherapy is an effective treatment for selected patients with bladder cancer, resulting in long-term disease control with preservation of normal bladder function. Modern radiotherapy treatment techniques offer the potential to improve cure rates and

reduce the adverse effects of radiation. The 5-year survival rates have been reported to be 35-71% for T1 tumors, 27-59% for T2 tumors, 10-38% for T3 tumors, and 0-16% for T4 tumors (L Sengeløv, H von der Maase 1999). The bladder is a mobile and hollow organ that changes size, shape and position during the course of treatment. This leads to significant variations in both the bladder wall and the position of the tumour, thus limiting the precision of conventional bladder radiotherapy (SD Collins, MM Leech 2018). To overcome this, large clinical target volume (CTV) versus planned target volume (PTV) margins of 1.5-2 cm are commonly used (Swindell R. Bowl N 1999). We performed radiosurgery with the "ELEKTA" linear accelerator with the first dose of radiotherapy administered 30-40 days after the last intravesical application. The daily dose was 1.8-2.0 Gy up to a total dose of 50-60 Gy. The mean volume of normal tissue irradiated using the linear accelerator ranged from 234 to 922 cm3 (mean 486 cm3) and the total dose for radical treatment ranged from 60-64 Gy.(Wright P , Redpath AT , Hoyer M 2008). There was no significant difference in the daily and total dose used as well as the volume of irradiated area in our study compared to other clinical reports. After the complete course of radiotherapy, only 3 patients experienced sporadic recurrences after BCG. All three patients were high-risk G3 with substantial multifocality and comorbidity. We performed subsequent transurethral resection with bipolar current in these patients. According to (Jennifer Y. Wo,William U. 2009), in 18 T1 and G3 patients undergoing adjuvant BCG therapy and radiotherapy to a total dose of 60-64 Gy. one resulted in cystectomy and 10 (59%) had no recurrence. In our study over 70% were relapse free. Trimodal therapy (TURB, intravesical and radiotherapy) has been evaluated in several prospective studies to achieve complete remission and good oncological response (Jonathan Khalifa and Stefan Soupio 2021). The benefit-risk ratio is commensurate with the latest technologies when operating with a linear accelerator (Cobo M, Delgado R 2006). Modern devices la radiotherapy offer a

high potential to improve cure rates and reduce adverse side effects (George L, Bladou F 2004). Several patients had to temporarily stop therapy due to general and local reactions from radiotherapy. We divided the patients into three groups according to the symptoms of radiation-induced cystitis. In (4;31%), the leading cause was pollakiuria, in (5;38%) hematuria, and in (4;31%) dysuria. All three symptoms were present in the three groups but their manifestation was to different degrees. Leading hematuria persisted for about 7 days. Patients had a three-way catheter placed on weak irrigation and were treated symptomatically (bloodletting, analgesics, NSAIDs and AB as needed). For local treatment of radiation hemorrhagic cystitis, we used sodium hyaluronate vials. We performed a 4-week course in 10 patients and an 8-week course in 3 patients. Cystoscopy revealed mucosal hyperemia and glomerulations in 13 patients and erosions in 3. After 4 weeks, nocturia and pollakiuria decreased by 40% and dysuria by 30%. Analgesic and NSAID intake decreased by 41%. Follow-up examinations at month 3 revealed that 10 patients had no evidence of hemorrhagic cystitis, but 3 patients had mild hyperemia without erosions. In the George Goucher and Fred Saad 2019 study, symptom assessment in radiation cystitis was done at 6, 12 and 18 months after therapy. Complete resolution of hematuria was noted in 88%, 75%, and 50% of patients in the hyaluronic acid group and in 75%, 50%, and 45% of patients in the no treatment group. This study also confirms our thesis that early use of sodium hyaluronate improves symptoms in hemorrhagic cystitis and leads to complete remission.

Discussion of Task 6.

To investigate the influence of comorbidities, diet and smoking on the occurrence and recurrence of bladder cancer, we identified three major groups. In the first, we included 380 patients with comorbidities, and in the second, 64 without comorbidities. The third group included 98 active smokers. The patients with comorbidities were those with hypertension, CHD, rhythm and conduction

disorders, COPD, cerebrovascular disease, obesity, diabetes mellitus, etc. All patients were without decompensated comorbidities. In the disease-free group, we noted the occurrence of recurrenceat 3, 6, 12, 18 and 24 months. Accordingly, this corresponded to 13, 11, 4, 2, and 5 patients. In the group with diseases, the results were 159, 81, 13, 31, and 25 patients. Comparing the results of the two clinical groups, it is clear that in the clinically healthy group, the chance of a new relapse decreased to 25% in the first 3 months. The total population with comorbid patients had a 4-fold higher risk of new tumor recurrence. According to (Yadi Lin, Yunyan Wang 2018), obesity was not significantly associated with overall mortality in bladder cancer (HR = 1.21, 95% CI: 0.97-1.52). The recurrence rate of bladder cancer was significantly higher in obese patients (HR = 1.76, 95% CI: 1.36-2.28) compared with normal weight patients. Stratification analysis showed that women had a higher risk of recurrence than men (HR = 1.17, 95% CI: 1.05-1.31). Analysis n revealed a linear relationship between BMI and risk of recurrence. Each kg/m2 increase in BMI was associated with a 1.3% increased risk of bladder cancer recurrence (HR = 1.01, 95% CI = 1.01 to 1.02). When assessing the effect of comorbidity on recurrence and survival, the presence of diabetes (HR: 1.5, 95% CI: 1.3-1.8), cardiovascular disease (HR: 1.3, 95% CI: 1.2-1.5), hypertension (HR: 1.1, 95% CI: 1.0-1.3), and lung disease (HR: 1.5, 95% CI: 1.3-1.7) significantly reduced survival (Catharina A. Goossens-Laan 2014). Treatment of comorbidities and prevention of their recurrence significantly reduces the risk of the formation of umbilical and recurrent bladder cancer. The Charlson comorbidity index is one of the most widely studied indices of 90-day perioperative mortality and overall and cancer-specific survival (Stephen B. Ashish M. Kamat 2019). In recent decades, there has been a growing interest in public health and disease prevention through lifestyle change. Various drugs have been widely used to reduce the risk of various diseases, including the occurrence of cancer. One such preventive treatment is the use of hydroxymethylglutaryl coenzyme A reductase

inhibitor (statins), (Erik Lundberg , Oskar Hagberg 2019). Some studies suggest that the population risk of bladder cancer with smoking is 50-65% in men and 20-30% in women. Current cigarette smoking triples the risk of bladder cancer compared to those who have never smoked (Neal D Freedman , Debra T Silverman 2012). In our study, we included 98 patients actively smoking more than 20 cigarettes per day. All made the decision to stop or reduce the daily number of cigarettes. We reported the occurrence of a new relapse at 3 mo in 33, at 6 mo in 22, at 12 mo in 5, at 18 mo in 4 and at 24 mo in 6 patients. At 3mo we had 66% relapse free from baseline group and at 12mo 85%. In this sample, smoking was a major contributor to relapse, but the different methods of trimodal treatment were secondary factors in generalizing the results. According to Chung-Hsin Chen, continuing smokers had a higher risk and chance of relapse compared with the quit or restricted smoking groups ($P<0.001$ and $P<0.058$, respectively).

Discussion of Task 7.

The development of a multimodal algorithm for the diagnosis, treatment, and follow-up of patients with superficial bladder cancer was the guiding principle of our clinical study. After summarizing the data over a 10-year follow-up period, we decided to propose an algorithm for the treatment and follow-up of patients with superficial bladder carcinoma. Guided by the guidelines of the Bulgarian Urological Society, the European Association of Urology. International Cancer Treatment Committee the idea of this extended algorithm and treatment recommendations to be multimodal emerged. Smoking increases the risk by about 50% because it contains multiple carcinogens. Exposure to carcinogens such as polycyclic aromas, amines, and chlorocarbons are risk factors. Elimination and reduction of exposure to these factors is of prime importance for disease prevention. Proper and competent treatment of co-morbidities are of paramount importance in the prevention of cancer.

Diagnosis is made by:

1.Physical examination

2.Clinical and laboratory examinations

2.Cytological examination of urine

3.Ultrasound, CT scan or MRI

4.Cystoscopy-gold diagnostic standard

5.Transurethral resection

Intravesical chemotherapy and/or immunotherapy is required in all patients after subsequent surgery. Subsequent highly focused radiotherapy is the next link in the multimodality model. The administration of immunotherapy in superficial carcinoma results in regression of the disease.

Recommendations for follow-up of bladder cancer (Leblanc et al . 1999 ; Zeeger et al . 2000 . ; Oge et al . 2000 . ; Holmang et al . 2001 ; Fujii et al . 2003 . ; Borhan et al . 2003 . ; Soloway et al . 2003 . ; Gofrit et al . 2006 . ; Sylvester et al . 2006)

1. Patients with TaT1 tumors at low risk of recurrence and progression should have cystoscopy at 3 months. If negative, the next cystoscopy is recommended 9 months later and then annually for 5 years.

2. Patients with TaT1 tumors at high risk of progression and those with CIS should have cystoscopy and urine cytology at 3 months. If negative, the next cystoscopy and cytology should be repeated every 3 months for 2 years and every 6 months thereafter for up to 5 years and then annually thereafter. An annual CT scan or MRI is recommended.

3. Patients with TaT1 tumors at intermediate risk of progression (about one-third of all patients) should have a follow-up schedule using cystoscopy and cytology that is tailored to objective and subjective factors.

4. During follow-up, in patients with positive cytology and no visible bladder tumor, biopsies or PDD biopsies and US (CT urography, prostate biopsy, urethral biopsy) are recommended.

Treatment recommendations for Ta,T1 and Tis according to risk stratification (Table 30).

Risk category	**Definition**	**Treatment recommendation**
Low risk tumours	Primary, edenic, TaG1 (PUNLMP, LG), <3 cm, no CIS	Immediate intravesical chemotherapy after TURB.
Medium risk tumours	All tumors not defined in the two adjacent categories (between low and high risk category).	For patients with a prior low recurrence rate (less than or equal to one recurrence per year) and an expected recurrence EORTC score <5, intravesical chemotherapy after TURB. At All patients either one year of full-dose BCG treatment (induction plus three weekly instillations at three, six and twelve months) or chemotherapy instillations (optimal regimen unknown) for a maximum of one year.
High risk tumours	Any of the following: T1 tumors; G3 (HG) tumor; CIS; Multiple, recurrent and sized (>3 cm) TaG1G2/LG tumors	Intravesical BCG full-dose instillations for one to three years,radiotherapy or radical cystectomy (for tumors at highest risk).
	Subgroup with highest risk tumors	
	T1G3/HG associated with concurrent CIS of the bladder, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra,	Radical cystectomy should be considered. In those who refuse or are suitable- intravesical BCG injections with full dose for one to three years and radiotherapy

Table 30. Risk stratification

VI. Conclusion

1. We created an algorithm to select patients for transurethral surgery in several groups.

2. The three methods of transurethral resection achieved comparably equal results, with minimal complications and good oncologic response.

3. Intravesical administration of various chemotherapeutic and immunotherapeutic therapies achieved good oncological control,minimal side effects and low local recurrence rate.

4. The application of radiation therapy with highly focused radiotherapy achieved good oncological control, minimal side effects and low local recurrence rate.

5. Administration of systemic immunotherapy achieved good oncologic response to no local recurrence.

6. There was a significantly higher % primary and recurrent p.bladder cancer in patients with concomitant diseases.

7. Smoking cessation or restriction reduced up to 60% occurrence and recurrence of urothelial carcinoma.

8. Changes in lifestyle and diet reduce the risk of new recurrence and disease progression.

9. We developed an algorithm for treatment and follow-up of patients with superficial carcinoma of the p. bladder.

10. A multidisciplinary approach to the management of urothelial carcinoma is believed to be at the forefront of new guidelines for the treatment of this

disease. Good oncological response and quality of life are paramount in the fight against cancer.

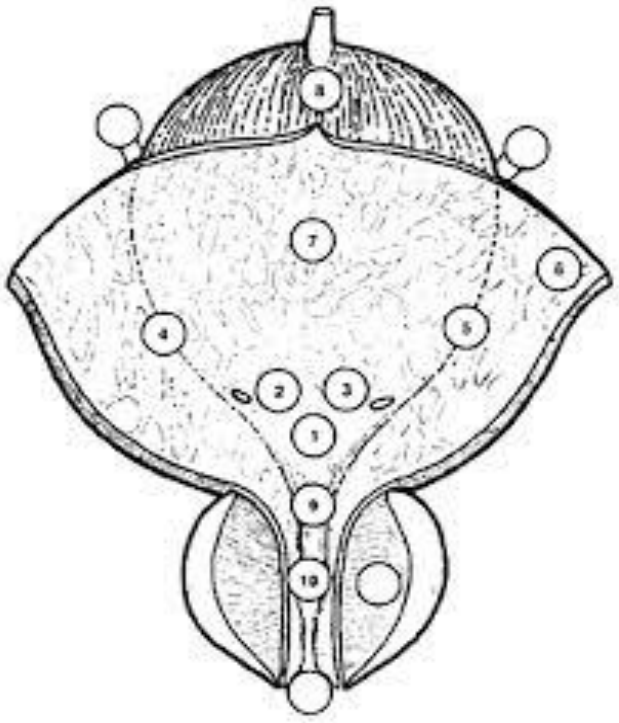
VII. Applications

PROTOCOL №

urethrocystocopy

Patient:

Adress:



1.Bladder triangle
2. Right ostium
3. Left ostium
4. Right lateral wall
5. Left lateral wall
6. Anterior wall
7. Rear wall
8. Dome
9. Bladder neck
10. Urethra

Size	0-1cm.	1-2cm.	>2cm.

Multifocality	

Characteristics	Papillary	Solid

Diagnosis:

RISK FACTORS ASSESSMENT CARD

To outpatient sheet No/date
Doctor (TIN, RHC/RHI facility number)
Patient (IDN, identification number)

PERSONAL ANAMNESIS	**FAMILY MEDICAL HISTORY**
smoking (Z72.0) number of cigarettes per day sedentary lifestyle (<30 minutes of physical activity per day) (Z72.3) colon adenoma(s) polyps of the colon (D12.6) colorectal cancer (C19) Crohn's disease (K50) ulcerative colitis (K51) celiac disease (K90.0) type diabetes mellitus type 1 (E10) type 2 (E11) previous evidence of dyslipidaemia (R94.8) daily consumption of fruit and vegetables (at least 100 g) regular intake of antihypertensive medication now or in the past history of elevated blood glucose Women ≥ 3 pregnancies worn out or first birth aged ≤ 17 yrs. Prolonged (more than 5 years) use of estrogens (contraceptives or hormone replacement therapy) (Z92.0) immunosuppressed (D80-D89) unvaccinated against HPV (for age group ≥ 18 and ≤ 25 years) + one of the following risk factors other cancer treated benign breast dysplasia (N60) early menarche (≤ 10 years of age)	Type 2 or Type 1 diabetes (grandparent, aunt, uncle or first cousin) (Z83.3) type 2 or type 1 diabetes (parent, brother, sister, own child) (Z83.3) early (under 55 for men - father, brother and under 65 for women - mother, sister) cardiovascular disease (CHD and MSD) (Z82.4) mother or sister with CHD (Z80.4) rectosigmoid cancer in one parent, sibling, child or two grandparents, grandparent, aunt, uncle, first cousin, nephew) (Z80.0) breast cancer in a mother, sister or daughter (Z80.3) prostate cancer (father, brother) in men over 40 (Z80.4)

first birth at age ≥ 35 yrs. Men PSA > 4.0 ng/ml in men over 40 years.	

DOCUMENT NO. 4

PATIENT (PARENT/GUARDIAN/CUSTODIAN) INFORMATION

Solid malignant tumours are diseases that originate in the body's tissues (excluding blood and lymph tissue), have a progressive course and may affect other organs and systems. The cause of their occurrence has not yet been fully established.

What are the most common complaints caused by solid malignant tumours?

The first manifestations are uncharacteristic: faintness, listlessness, vague fever, mild tenderness in the affected organ, heaviness in the abdomen, alternating diarrhoea and constipation, weight loss, chest pain, shortness of breath or persistent cough, reduced performance. Vague masses are found in various parts of the body, enlarged lymph nodes - most often in the cervical or axillary region, they are not painful and gradually increase. In men, there may be urinary urgency, especially at night, as well as pain in the testicles.

What methods and procedures are needed to diagnose a malignant tumour?

Preliminary tests for diagnosis are carried out by your GP in the relevant laboratory, where blood will be taken from your vein. You will then have ultrasound and X-ray examinations of various parts of your body. If abnormalities are found, you will be referred to an appropriate specialist (surgeon, gynaecologist, urologist, pulmonologist, otorhinolaryngologist, etc.). He/she will appoint further specialized examinations. The diagnosis of a malignant tumour will be made after performing a biopsy of the suspicious area or lymph nodes or tissues involved by the tumour. To confirm the diagnosis, histological evaluation of the biopsy should be performed by a pathologist, as well as additional immunohistochemical studies if necessary. If a malignant tumor is found, all of your studies will be presented to an oncology committee, which includes specialists from various fields to discuss the best method or combination of different methods for your treatment. You will be referred to the appropriate specialist (surgeon, radiotherapist or chemotherapist) to carry out your treatment. In the consultation room of the relevant clinic/department, the specialist will evaluate the laboratory and instrumental tests performed, prepare the documents for admission to the clinic/department and assign you a day and time for admission (except in cases of emergency).

How are solid malignant tumours treated ?

The treatment is complex, with surgical, radiation or drug treatment applied in different sequences. The main local treatments are surgery and radiotherapy. Drug treatment is used in certain cases before surgery to reduce the volume of the tumour and to preserve the operated organ. In some cases, when it is found that the tumour cannot be removed surgically because of its penetration into surrounding organs or in the presence of disseminations, chemotherapy most often remains the only method of treatment. You will be given detailed instructions about the medications that are used for your treatment. Treatment is carried out by administering several courses of chemotherapy with breaks in between, after which the effect achieved is reported. What complications can occur when I have systemic anti-tumour drug treatment? Treatment should only be carried out in highly specialised

chemotherapy clinics and departments where there are qualified staff, the necessary drugs and the appropriate conditions for their administration. Complications of the treatment are mainly related to the antitumour drugs used:

- sterility (often reversible);

- listlessness, nausea, vomiting, diarrhoea, change in taste sensations

- hair loss - occurs with most drug combinations and is reversible - hair grows back after discontinuation of treatment;

- decrease in the number of blood cells (leukopenia, thrombocytopenia, anaemia), which most often recovers in the breaks between courses, and less often requires the administration of growth factors (of the white or red blood line).

- disruption of the menstrual cycle;

- inflammation of the vein (phlebitis) into which the drugs are introduced. It is expressed in local redness, pain, increase in local and general temperature.

- Skin rash, nail changes, discoloration of skin and mucous membranes.

- Change in urine colour immediately after intravenous infusion

- Hypersensitivity reactions

Symptomatic remedies are available to overcome the above adverse drug reactions.

Please contact the doctor prescribing your treatment for further information.

Attending physician **Patient**

Patient: first name surname last name

Date of birth:		ID No./APR No:		Age:		
Height (cm):		Weight:		Body surface area (m2):		
Creatinine:		Department, Name and Code:		Date - start of therapy:		
Cycle No:		Chemotherapy regimen:				

Date - Day(s)	No.	Hour of application	ATC	Medicinal product - brand name	Medicinal form	Route of application (iv, sc, po, intracavitary, intravesical, etc.)	Standard dosage	Individual dose (mg/mcg/IU/MIU/MU)	Dose reduction in %	Adjusted individual dose (mg/mcg/IU/MIU/MU)	Carrier	Patient container (glass jar, PVC jar, infusion bag, syringe, elastomer pump, etc.)	Volume of finished solution (ml)	Time/ Application rate (h ? ml/h)
Date:	1													
	2													
	...													

Attending physician: ..... (signature) Assigned to: ..... (date)

First name Last name

Prepared by. First Name Last Name Last Name ..... (signature)

Verified by: mag.-pharm. First Name Last Name ..... (signature)

Therapeutic protocol sheet №

Patient report COMPASS

Rx A: Plan Report

Monaco 5.11.03

Hospital/Clinic:	KOC-VRATSA	Doc Number:	Rx A: 19220220822.111217.001
Patient Name:	SAVOV^ILIYA	Save Plan Date/Time:	Aug 22, 2022 11:20:31
Patient ID:	4306032169	Print Date/Time:	Aug 22, 2022 11:30:57
Plan Name:	CT1:SS_CT1:CaVesUrinae60	Workstation ID:	MONACO 192.168.33.136
Description:			
Comment:	ALL COORDINATES ARE REPORTED IN THE DICOM COORDINATE SPACE.		

StudySet Information

Studyset ID: CT1 **# of Slices:** 126 **Pixel Size:** 0.10 **Scan Orientation:** Head First Supine

Plan Information

Treatment Orientation: Head First Supine

Max Dose in Plan (Gy): 66.028

Max Dose Location (cm): X = -3.62 Y = -17.65 Z = -47.47

Grid Information

Grid Spacing (cm): 0.30 **Assigned CTtoED File:** DICOM3.VratsaN

Calculate Dose Deposition to: Medium **# of Calculation Points:** 1683612

Force entire volume to be treated as water: No

Prescription Information: [A]

Rx Site	Prescribe To:	Rx Dose (Gy)	Fractional Dose (Gy)	Number of Fractions
Ves.Urinae60	100.00% of ptv	60.000	2.000	30

Actual Dose(Gy): 52.601

Rescale: No user normalization applied

Algorithm: Monte Carlo Photon

Statistical Uncertainty (%) per Calculation: 1.00

Delivery Mode: VMAT

Beam Information

Scan Reference Coordinates (cm): X = -0.26 Y = -19.71 Z = -49.97

Seq.	Description	Treatment Unit	Modality	Energy	Gantry (deg)	Coll. (deg)	Couch (deg)	Isocenter X(cm)	Y(cm)	Z(cm)	# of Segs	MU/Fx
1	AR60	Linac1	Photon	10.0 MV	180.0/-360.0	0.0	0.0	0.58	-22.95	-47.77	255	1034.28
2	S0	Linac1	Photon	6.0 MV	0.0	0.0	0.0	0.58	-22.95	-47.77	1	0.00
3	S90	Linac1	Photon	6.0 MV	90.0	0.0	0.0	0.58	-22.95	-47.77	1	0.00
										Total:	257	1034.28

Approved by:

Name:_____ Signature:_____ Date:_____

Page 2 of 5

EORTC risk tables for predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer

The software provided applies the EORTC scoring system and risk tables for stage Ta T1 bladder cancer as published in the article:

Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DWW and Kurth KH. Predicting recurrence and progression in individual patients with Ta T1 stage bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC studies. European Urology 49: 466-477, 2006.

They allow the user to estimate the likelihood of recurrence and progression in patients with stage Ta T1 bladder cancer based on six different factors:

- The number of tumors

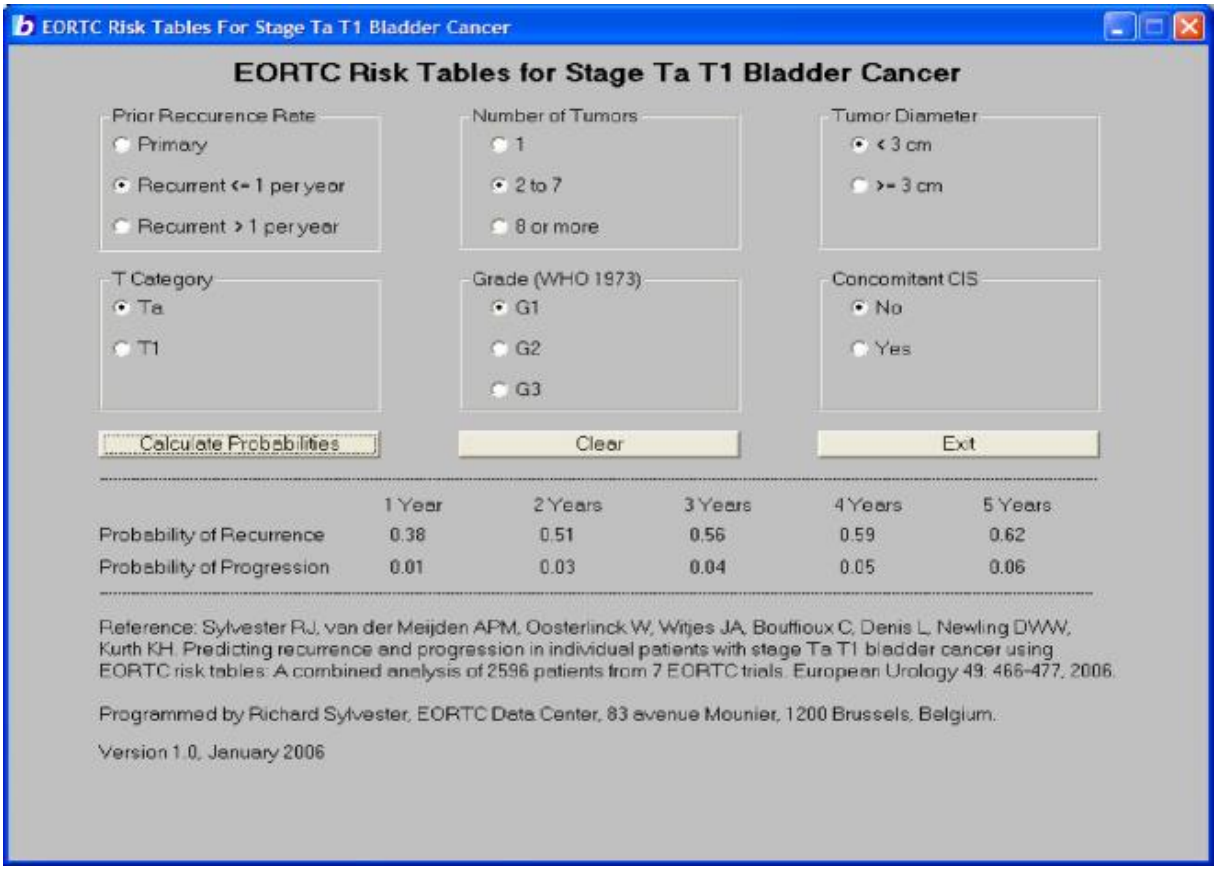
- Tumor size

- Incidence of previous recurrence

- T category

- Concomitant carcinoma in situ

- Grade



VIII. References used

IX. Contributions of the thesis

1. In this dissertation, an in-depth analysis of the occurrence of primary and recurrent superficial urothelial carcinoma of the bladder was performed and patients were divided into several groups according to different criteria. This enabled the identification of prognostic factors to reduce the risk of disease progression.

2. We performed an in-depth comparative analysis using local chemotherapy and/or immunotherapy versus established standard surgical treatment.

3. We described a new conservative method for the treatment of recurrent verrucous tumors by radiosurgery. We thoroughly studied its complications and outcomes.

4. We applied systemic immunotherapy in patients with high oncological risk of disease progression.

5. We created an algorithm for multimodality treatment and follow-up of patients with bladder tumor.

X . Publications related to the thesis

1. Nikolay Nikolov, Nikolay Kolev, Ivan Malkodanski, Alexander Lyubenov, Vladislav Dunev, Blagovest Bechev, Boyan Atanasov. Intravesical therapy of radiation cystitis with sodium hyaluronate in patients with superficial bladder carcinoma undergoing highly focused low-dose radiotherapy. Clinical Urology" ISSN 2738-778X, Volume 1, Issue 2/2021

2. Nikolay Nikolov,Vladislav Dunev,Boyan Atanasov.Laser-induced resection of superficial bladder carcinoma-initial experience. Clinical Urology ISSN 2738-778X,Volume 2,Issue 1/2022

3. Nikolay Nikolov.Radiotherapy for recurrent stage T1-G3 bladder carcinoma-comparative analysis. Urology and endourology ISSN 2535-0560,volume 28,issue 1/2022

4. Nikolay I. Nikolov,Vladislav R. Dunev,Angel A. Anatoliev,Martin B. Stoykov,Boyan S. Atanasov,Journal of biomedical and clinical research ISSN 1313-6917,vol.15 No 1/2022

5. N.Nikolov, N.Yordanov. Nutrition in urothelial carcinoma. Behavior in urothelial carcinoma; textbook 2020; Texts for continuing medical education ; ed. Д. Kalev; Varna ; 2020; ISBN 978-619-7094 -51-0; pp. 177-187

6. Malkodanski I., Atanasov B., Radev Vl., Bogdanov S., Genov P., Stefanovski P., Radev R., Nikolov N. Ultrasound-guided obturator nerve block in transurethral resection; Anaesthesiology and intensive care, vol. 4/2019, Year XLVIII, p. 30-32., ISSN 1310-4284, (Scopus)