OVIDIUS UNIVERSITY OF CONSTANȚA
MEDICAL DOCTORAL SCHOOL
FIELD: MEDICINE

PhD THESIS ABSTRACT

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PhD STUDENT: PREDA COSMIN-FLORIN

CONSTANȚA 2024

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PELVIC TUMORS WITH BLADDER STARTING POINT CURRENT DIAGNOSTIC AND THERAPEUTIC ELEMENTS

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1. Research motivation:

Research purpose: To determine how bladder carcinomas occur, to determine the most common locations and the current therapeutic modalities for them.

Research objectives:
Identification of causes and factors leading to bladder tumours (internal factors, external factors).
Morpho-pathological study of bladder tumours, morpho-pathological grading, TNM staging, determination of main sites of pelvic invasion, if applicable.
Determination of the role of genetic factors and association of bladder tumours with nicotine and ethyl alcohol consumption and other associated comorbidities.
Establish the principal means of investigation of bladder carcinomas.
Treatment regimens used, surgical versus chemotherapeutic treatment, determination of efficacy of adjuvant BCG treatment, instillations.

Anatomy notions
The urinary bladder is a muscular reservoir where urine is collected, located retro-symphyseal.
A normally functioning bladder is an efficient coordination between musculoskeletal, neurological and psychological functions, which allow the bladder contents to be accumulated and discharged.
Continence is achieved by synergistic relaxation of the detrusor muscle and contraction of the bladder neck and pelvic floor muscles.

Urinary bladder

The urinary bladder, a cavitary organ located subperitoneal, undergoes a significant morphological evolution from childhood to puberty. Initially located supra-symphyseal in childhood, it migrates to the pelvic region and later, at puberty, retreats to the retro-symphyseal region. Its normal urine storage capacity varies between 450-500 ml, with a higher capacity in women (maximum 700 ml) and lower in men (around 300 ml). However, in pathological conditions, this capacity can vary considerably, ranging from 10-20 ml to several litres.
The structure of the bladder wall histologically has the following layers from inside to outside:

Mucosa: Made up of a transitional type epithelium called urothelium, consisting of 5-7 layers of cells sitting on thin basement membrane and chorion. The chorion or almina propria has a trophic role for the transitional epithelium and is composed of lax connective tissue containing elastic fibres, abundant vascular network, lymphatic vessels, sensory nerve structures and smooth muscle fibres that make up the muscularis mucosa. In women, the bladder trigone is covered by a non-keratinised squamous epithelium subject to cyclic hormonal influences, similar to the vaginal mucosa.

Muscle (bladder detrusor): made up of fibres arranged in three layers:

- external or longitudinal layer;
- middle or circular;
- internal or longitudinal.

The muscles describe, as a whole, a spiral or helical path. In the case of subvesical obstruction, hypertrophy of muscle fibres in the outer layer develops, so that the mucosa bladder takes on the appearance of 'bladder columns', between which are depressions called 'bladder cells'. Bladder cells are areas of low resistance where, under pressure, bladder diverticula can form.

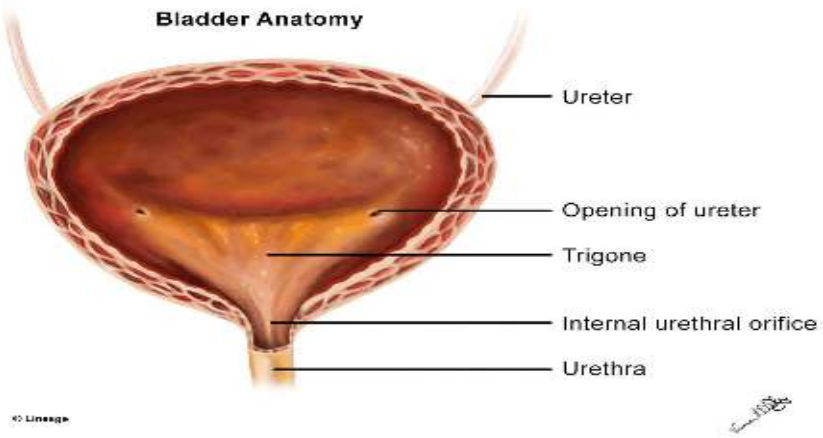


Fig 1 - Urinary bladder anatomy

Bladder tumours, diagnostic elements

I. Introduction

Neoplastic pathology is caused by a number of factors:

A. Exogenous

B. Endogenous

A. Exogenous factors:

1. Physical carcinogenic agents:

a) Ionising radiation: gamma, beta, alpha

Causes ionization of nitrogenous bases and DNA strand break.

b) Ultraviolet radiation

c) Asbestos

d) Foreign bodies: plastic membranes and tubing, glass fibres, dextran polymers

e) Small and repeated traumas

2. Chemical carcinogenic agents

a) Industrial products:

Inorganic: cadmium - causes bladder neoplasm

Organic: nitrosamines: colon cancer

Polycyclic aromatic hydrocarbons - digestive cancers, bladder cancers, sarcomas

Aniline rubbers and dyes: bladder neoplasm

b) Pharmaceutical products, of which:

- Phenacetin
- Diethylstilbestrol which leads to a significant risk of uterine, vaginal, breast and ovarian neoplasms,
- Cyclophosphamide which will increase the risk of bladder neoplasm
- Chloramphenicol, etc.

c) Food products

- Pyrolysis of amino acids in meat (grilling) - colorectal neoplasms
- Animal fats and refined sweets - breast, ovarian and endometrial neoplasm.

d) Beverages:
- Soluble coffee contains methylglyoxal and causes colorectal, ovarian, endometrial neoplasia
- Alcohol: whisky, cognac - contain mutagenic substances in suspension found in the residues obtained by evaporation.
e) Smoking - associated with urothelial carcinomas

3) Biological carcinogenic agents
a) Parasites:
- Schistostoma haematobium - interstitial cystitis with squamous metaplasia of the bladder urothelium and development of squamous cell carcinoma
- Trichomonas vaginalis closely related to cervical and vaginal cancers
b) Mycotoxins representing metabolites of certain moulds
c) Viruses:
- Human papilloma viruses (HPV) cause squamous cell carcinomas
- Human herpes simplex virus etc.

B) Ebdogenous factors
1) Immunological factors
Antigenically, a tumour is a cellular mosaic, with the highest antigenic potency in the G1 phase of the cell cycle. Tumour antigens are histotypic and specific for a particular tumour type and are considered tumour markers that contribute to accurate diagnosis and patient follow-up.

- CA 19-9 - adenocarcinoma of the colon
- CA-125 - ovarian neoplasm
- PSA - prostate specific antigen - prostate neoplasm
- Beta HCG - teratomas and trophoblastic tumors

2) Genetic factors
There are 3 major theories explaining the mechanisms of carcinogenesis:
Somatic mutation theory - accepts the existence of structural changes, induced by mutagenic agents, in genes encoding cell growth and differentiation.

Epigenetic theory - admits some functional changes in the control of gene expression, with the appearance of abnormal proliferations.

Genetic theory - brings together somatic mutation theory and epigenetic theory.

Urothelial (Transitional) Carcinomas

Represents about 90% of tumours of the bladder, urethra and ureter.

The name transitional corresponds to the transitional epithelium name that is used for ureothelium [5].

Ethiology

Protoncogene activation → oncogenes - dominant **ras**, **c-myc** interfere with normal cell growth control mechanisms → increased proliferation

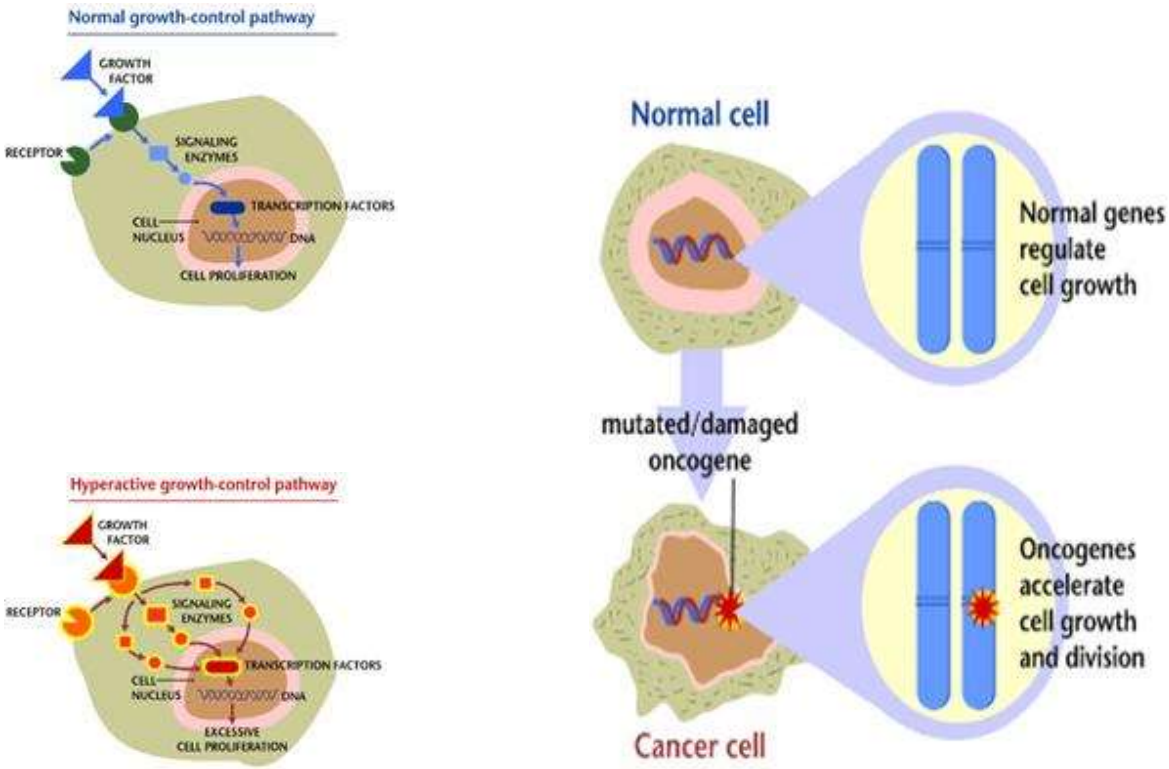
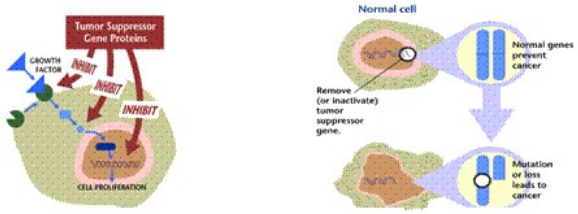


Fig 2 Oncogenes activation mechanism

Inactivation (deletion) of tumour suppressor genes - recessive **p53, Rb, p15, p16** - regulates cell growth, DNA repair, apoptosis;

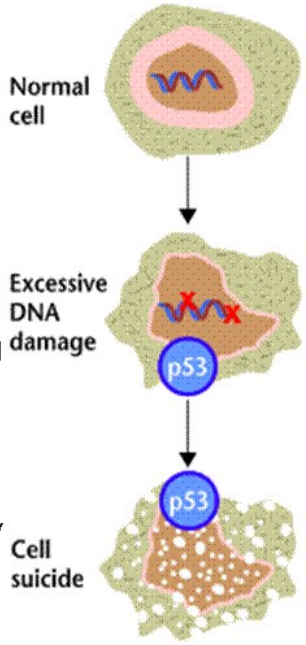
- E.g.: - deletions 9p (p15, p16) - superficial, low grade tumours

- deletions 17p (p53) - high grade invasive tumours



- *p53*

- wt p53 - transcription factor, triggers altered DNA cell apoptosis;
- moved protein - altered DNA cells end the cell cycle
- increased cell proliferation / genetic instability (mutations)



- *Rb*

- pRb normal active / hypophosphorylated connects the E2F transcription factor;
- in the transformed cell - pRb hypophosphorylated / constitutionally inactivated, releases E2F, the cell passes easily the G1-S control point, runns quickly thourgh the cell cycle
- increased cell proliferation

- *p15, p16*

- inhibits cyclin-dependent kinases, which phosphorylate pRb;

Fig 4 - Mechanism of tumor suppressor gene deletion [6]

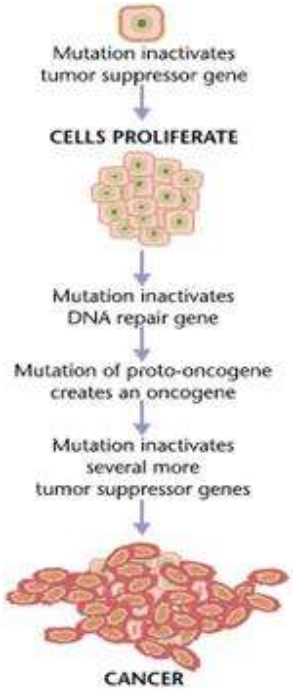


Fig 3 - Amplification of normal genes - encoding growth factors or their receptors (EGFR) [6]

Inactivation of DNA repair genes

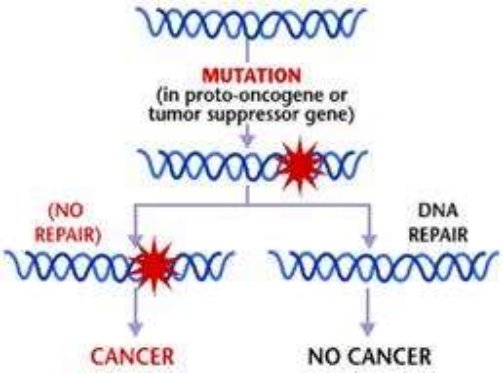


Fig4 – Inactivation mechanism of DNA repair genes

Professional exposure

- aromatic amines - skin, respiration, food

approx. 20% of bladder tumours in the US, long latency (30-50 years)

- aniline dyes - Rehn 1895

- 2-naphthylamine, 4-aminodiphenyl, 4-nitrodiphenyl, 4-4-diaminodiphenyl (benzidine)

combustion gases, soot, food nitrites/nitrates

Smoking (4x) - nitrosamine, 2-naphthylamine, 4-aminodiphenyl

- N-acetyltransferase 2 - detox. 4-aminodiphenyl - slow/fast acetylators
- Glutathione S-transferase M1 - detox. carcinogens
- P-450 1A2 (CYP1A2) cytochrome - aromatic amine demethylation
- Analgesic abuse - phenacetin, 5-15 kg in 10 years, high latency
- Bilharziasis (Schistosoma haematobium)
- Human papillomavirus (HPV)
- Irradiation of the pelvis (2-4x)
- Cyclophosphamide (9x) - 6-13 years, acrolein, Mesna uroprotectant
- Inverted papilloma - frequently associated with transitional carcinomas [6]

These may be tumors:

- papillary
- solid-infiltrative
- mixed

The vast majority however are papillary tumours.

Papillary tumours can be solitary, but are usually multiple.

Macroscopically:

They appear as reddish exophytic lesions, ranging in size from 1 to over 5 cm, some of which are friable and have haemorrhagic areas. For the most part, these lesions develop on the posterior and lateral walls of the bladder. Histopathologically, they range from well-differentiated to poorly differentiated and anaplastic papillary tumours.

Microscopically:

They are divided into high grade and low grade urothelial carcinomas.

Low grade papillary urothelial carcinomas: papillary structures are lined with malignant transitional epithelium with minimal cytological atypia, nuclei are moderately hyperchromatic with minimal mitotic activity. In 10% of cases there is invasion of lamina propria or muscularis propria.

High grade papillary urothelial carcinomas: as a difference, hyperchromic and pleomorphic nuclei are found. They are more aggressive causing damage to the lamina propria and subsequently to the muscle.

Staging of bladder carcinomas

TNM Staging (AJCC-2010)

T – primary tumor

Tx – the primary tumour cannot be assessed

T0 – there are no signs of primary tumour

Ta – non-invasive papillary carcinoma (limited to the urothelial layer)

T1s – transitional "in situ" cell carcinoma - a flat tumor form

T1 – the tumor invades the subepithelial connective tissue (chorion, lamina propria)

T2 – the tumour invades muscularis propria

T2a – superficial invasion (1/2 internal)

T2b – deep muscle invasion (1/2 external)

T3 – the tumor invades the perivesical fat

T3a – microscopic invasion of perivesical fat

T3b – macroscopic invasion of perivesical fat

T4 – the tumour invades the pelvic organs, pelvic or abdominal wall

T4a – tumor invades the prostate, uterus, vagina

T4b – the tumour invades the pelvic or abdominal wall

N - lymph node

Nx – regional lymph nodes cannot be assessed

N0 – there are no metastases in the regional lymph nodes

N1 – represented by a single metastasis in a single pelvic lymph node (hypogastric, obturator, external iliac or presacral)

N2 – lymph node metastasis in more than one pelvic lymph node (hypogastric, obturator, external iliac or presacral)

N3 – metastasis in the common iliac lymph nodes

M - metastasis

M0 – there are no remote metastases

M1 – there are remote metastases

Staging

Stg. 0a	Ta	N0	M0
Stg. 0is	Tis	N0	M0
Stg. I	T1	N0	M0
Stg. II	T2a, b	N0	M0
Stg. III	T3a, b, c	N0	M0
T4a			
Stg. IV	T4b	N0	M0
Any T	N1,2,3	M0	
Any T	Any N	M1	

Clinical staging

Primary tumour assessment in bladder cancer requires a comprehensive and multidisciplinary approach, involving several specific procedures and techniques. An essential aspect of this process is the bimanual examination under anaesthesia, which takes place before and after endoscopic surgery such as biopsy or transurethral resection. Histological confirmation of the presence or absence of the tumor is essential in establishing the correct diagnosis.

Bimanual examination post endoscopic surgery serves as an important indicator of clinical staging. Identification of changes such as thickening of the bladder wall, presence of a mobile or fixed mass may suggest the presence of T3 and/or T4 disease, providing valuable information for determining the local spread of disease.

Specialised imaging techniques are used to assess extra-vesical extension of the primary tumour and to analyse the lymph nodes. These may include magnetic resonance imaging (MRI), computed tomography (CT) and/or positron emission tomography (PET-CT), which are integrated into the clinical staging process. These investigations provide detailed information about the location and size of the tumour, as well as any lymph node involvement.

In situations where distant metastases are indicated for assessment, additional investigations, such as imaging studies of the chest, and biochemical and isotopic studies are used for early

detection of possible remote metastases. This integrated and multidisciplinary approach contributes to an accurate staging of the disease and the development of a personalised treatment plan for each patient.

Pathological staging

Detailed assessment of the primary tumor requires microscopic examination and confirmation of extension, which are essential for correct staging of bladder cancer. Total cystectomy and lymph node dissection are generally essential procedures for accurate staging; however, it is important to note that pathological staging classification should also be applied to specimens obtained by partial cystectomy. The assessment of laterality does not influence the classification of stage N (ganglionic).

The classification system includes two main categories for urothelial histologies:

LG - Low Grade:

- Low grade tumors are characterised by less atypical cells and slower growth.
- They may have a more organised architecture and are generally associated with a better prognosis.
- Patients with low-grade tumors may have a lower risk of recurrence and progression.

HG - High Grade:

- High grade tumors are characterized by more atypical cells, with faster growth and more disorganized architecture.
- They are associated with a poorer prognosis and an increased risk of recurrence and progression.
- Careful treatment and monitoring are often necessary in patients with high grade tumors.

If a classification system is not specified, the following system is generally used, which is the model developed at WHO level.

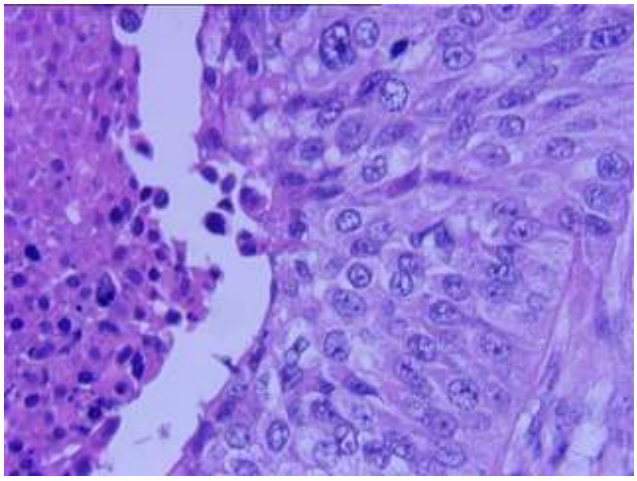


Fig 5 – Microscopic Appearance of Urothelial Carcinoma

Clinical manifestations specific to malignant tumors of the bladder are represented by:

- Total, spontaneous haematuria
- Pyuria
- Dysuria - marked by difficulty, dryness when urinating
- Polachyuria

Recurrent lower urinary tract infections (cystitis) characterized by hypogastric pain, dysuria, polyuria, urinary incontinence, hematuria, nocturia

Diagnostic

The diagnosis of bladder tumour will be made on the basis of clinical examination symptoms and paraclinical investigations such as urography, ultrasound, cystoscopy, CT (computed tomography), MRI (magnetic resonance imaging) and BTA-stat (bladder tumour analysis). Confirmation of this diagnosis will be made by biopsy, histopathological examination and cytology.

Paraclinical investigations

The description of the paraclinical investigations is complete and detailed. Here is more information about each of them:

1. Cystoscopy:

- Reference investigation for the visualisation of bladder tumors.
- Provides details of the appearance, size and extent of tumor infiltration of the bladder lining.
- It is mainly used before surgery to guide treatment.

2. Urography:

- Uses contrast agents to highlight the anatomy of the upper and lower urinary tract.
- Tumor formations show a lacunar image appearance on urography.
- It indicates dilatation of the urinary tract, which may suggest obstruction or other tumor-associated changes.

3. Ultrasound:

- Non-invasive method of examining the urinary tract and bladder tumors.
- Malignant bladder tumor appears hypoechogenic on ultrasound, which may indicate a solid lesion.

4. BTA-Stat:

- Rapid urine test that detects human complementary protein-related factor H (HCFHrp).
- It can be used for rapid diagnosis of bladder neoplasm in suspected individuals.

5. Histopathological examination:

- It is performed by bladder biopsy and allows the identification of malignant cells in tumor tissue fragments.
- Provides essential information for the diagnosis and histological grade of the tumor.

6. Free-flow urinary cytology:

- Detects cancer cells in fresh urine or bladder lavage fluid.
- It can be a useful way of screening and monitoring patients with bladder tumors.

Investigations to assess spread and metastases include:

- Lymphoscintigraphy: identifies lymph nodes invaded by the tumor process.
- Bone scintigraphy: Identifies bone metastases.
- Computed tomography (CT) and magnetic resonance imaging (MRI): Provides detailed images to assess the extent of tumor lesions and identify metastases.

Cystoscopy is an essential procedure in the evaluation of bladder pathology, providing the doctor with valuable information about its condition and characteristics. During this investigation, the

bladder environment is explored, ranging from clear to turbid, and normal staining or the presence of haematuria is analysed.

One of the important aspects of cystoscopy is the assessment of bladder capacity. After emptying the bladder, urine collection for cytological and bacteriological examinations is also allowed. Subsequent filling of the bladder facilitates analysis of its walls, allowing assessment of its internal appearance.

Cystoscopy also provides insight into the symmetry of the bladder cavity. Asymmetric, rigid or protruding areas that do not relax properly can be identified. The appearance of the orifices present in the bladder, including the ureteral orifices, and the presence of any stones or foreign bodies are essential details examined during the procedure.

A crucial element of cystoscopy is the assessment of the appearance of the bladder lining. The presence of specific changes is examined, which may suggest various conditions, including inflammatory or tumor lesions. In the context of detecting such changes, diagnostic and therapeutic decisions relevant to patient care can be made.

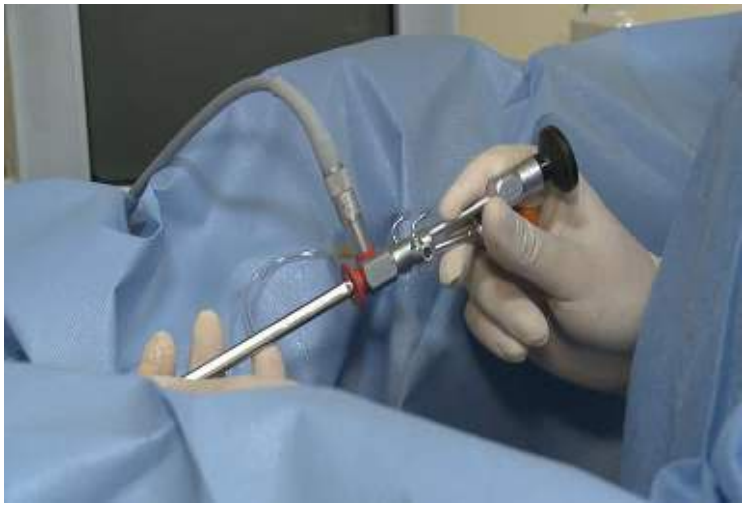


Fig 6 Cystoscope

Therapeutic options

The treatment of bladder tumors is a complex challenge and surgical approach can be a key option, either as a single procedure or in combination with adjuvant therapies such as cytostatic medication (chemotherapy), administered intravesically, radiotherapy or biological therapy with BCG vaccine.

Chemotherapy, which uses chemicals to destroy tumor cells, can be implemented at different phases of treatment, either before or after surgery, and is essential in preventing recurrence and improving outcomes.

Radiotherapy, based on the administration of fractionated doses of high-intensity X-rays (Roentgen) or different types of radiation, is a therapeutic option that can be applied before or after surgery, depending on the stage and characteristics of the tumor, bringing significant benefits to patients.

Biological therapy, with a focus on stimulating the immune system, plays a crucial role in triggering a specific inflammatory response in the urothelium, thus helping to stop or slow down tumor recurrence.

These therapeutic approaches, depending on the particularities of each case, can be combined to achieve the best results. It is important to assess and adjust treatment according to the individual patient's response and disease progression, ensuring a personalised and effective approach to bladder neoplasia.

Initial treatment

Surgery is an essential treatment mode for most bladder cancers, and surgical options vary depending on the size, location and stage of the tumors. Here are some surgical procedures used in the treatment of bladder cancer:

- Electrocautery in cystoscopy. Small, superficial tumors can be treated by cautery using a low-voltage electrocautery during cystoscopic examination. This approach can be effective for localised lesions.
- Transurethral resection (TUR): Indicated in the treatment of large, superficial tumors or those that have penetrated deeply but no remote extension is present. This procedure involves the removal of tumor tissue using an instrument inserted through the urethra.
- Cystectomy is the total resection of the bladder. Recommended in advanced stages of cancer confined to the bladder or in high grade tumors. However, it is not always indicated in elderly patients with associated chronic diseases. Cystectomy can be partial or radical.
- Partial cystectomy: Involves the removal of a section of the bladder and is a suitable option for a single tumor invading the bladder wall in one region. This type of surgery has the advantage of preserving most of the bladder.

- Radical cystectomy: This is the complete removal of the bladder and can be used for more extensive cancers or cancers that have spread outside the bladder. This surgical procedure usually involves an incision from the umbilicus to the pubic bone, with removal of the bladder and, in some cases, other adjacent affected organs.
- Laparoscopic radical cystectomy: A modern variant of radical cystectomy, involving the use of laparoscopic techniques, thus minimizing incision size and postoperative recovery.

Endoscopic treatment of non-invasive bladder tumors has evolved and transurethral resection of bladder tumors (TUR-v) remains an essential intervention, with the aims of establishing an accurate diagnosis and complete removal of visible lesions. However, therapeutic alternatives are also being explored for tumors with specific features, as mentioned in medical practice guidelines.

Chemotherapy

Chemotherapy is a complex therapeutic mode using drugs with a destructive role on neoplastic cells, with different applications depending on the type, stage and location of bladder cancer.
For superficial bladder tumors, an effective approach is the intravesical administration of drugs. Through a catheter, these substances are introduced directly into the bladder by instillation, having a direct impact on superficial lesions.
In recent years, the field of bladder cancer treatment has seen significant progress with the introduction of anti PD-1 and PD-L1 agents. Pembrolizumab, one such agent, has received approval based on excellent results in phase 3 clinical trials demonstrating extension of overall survival. Four other immunological agents - atezolizumab, durvalumab, nivolumab and avelumab - received accelerated approval due to the high objective response rates seen in a significant percentage of patients, opening new perspectives in the treatment of advanced or metastatic urothelial cancers.

Chemotherapy is used in the treatment of bladder tumors to limit tumor progression and reduce symptoms. The chemotherapeutics used have the ability to destroy the malignant cell population or stop it from progressing. Chemotherapeutic drugs are administered orally, intravenously or instilled intravenously (via a catheter).
Chemotherapy is a systemic treatment because it enters the circulation and will spread to the tumor where it will destroy the malignant cell population. Commonly used chemotherapies

include:
- Doxorubicin, epirubicin, valrubicin belonging to the anthracycline group
- MVAC - is a combination of several chemotherapies such as methotrexate, doxorubicin, vinblastine and cisplatin. Methotrexate is a cytostatic that effectively slows or stops the multiplication of neoplastic cells and is frequently used in combination with other chemotherapeutic agents. Cisplatin contains a heavy metal derived from platinum that effectively blocks the multiplication of neoplastic cells.
- Gemcitabine blocks the multiplication of malignant cells and stops the growth of the tumour bed
- Paclitaxel or carboplatin.

Intravenous chemotherapy uses the following drugs:
- Mitomycin - C Bleomycin instilled intravenously via catheter prevents tumour recurrence rate post surgical treatment
- BCG - Calmette-Guerin bacillus triggers an immune or inflammatory response in the bladder wall leading to "bacillary cystitis" and is part of biological therapy.

Next, chemotherapeutics are used either alone or in combination and can be instilled directly into the bladder using an intravesical catheter. Adjuvant chemotherapy can also be used post transurethral resection (TUR-V). Chemotherapy also becomes a treatment option when surgical sanction cannot be applied.

Most chemotherapies used in the treatment of urothelial carcinomas will have various side effects, and it is up to the doctor to communicate information to the patient about possible side effects. A healthy lifestyle combining a balanced diet, sufficient rest and even exercise can help manage symptoms.

In neoadjuvant treatment, interferon or other selected chemotherapies are administered prior to the application of the specialised surgical sanction.

Radiotherapy

Radiotherapy with X-rays or other high-energy radiation is a standard method of treatment for certain types of bladder cancer. This therapy is based on the principle of using ionising radiation to destroy malignant cells, preventing them from dividing and growing. In bladder cancer,

radiotherapy can be given for curative or palliative purposes, depending on the stage of the disease and the therapeutic goals.

Biological therapy

Biological therapy is an innovative treatment mode for bladder cancer, based on the use of molecules that stimulate the immune system's reaction against tumor cells. These molecules generally act on specific markers presented by the cancer cells, thus triggering a targeted immune reaction against them.

In particular, biological therapy is frequently used in the treatment of superficial tumor formations of the bladder. It can be administered after surgery such as transurethral resection (TUR) or other procedures to remove superficial tumours. The aim of postoperative biologic therapy is to prevent the recurrence of bladder cancer, reducing the chances of tumors returning and improving long-term prognosis.

Molecules used in biological therapy may include immunotherapies such as pembrolizumab, atezolizumab, durvalumab, nivolumab and avelumab. These substances work by blocking certain immune-system avoidance mechanisms of cancer cells, thus allowing the immune system to identify and destroy them more effectively.

Other types of treatment

Radiotherapy is a standard therapy for various stages of bladder tumours, but is sometimes used in combination with specialist surgical treatment. Radiotherapy as a principle consists of the use of high-intensity X-rays to eradicate malignant cells or to shrink the original tumour. Radiotherapy may also be used for palliative purposes to reduce the effects of evolving tumor masses.

Photodynamic therapy consists of administering molecules that are photosensitive. This substance is selectively retained in the tumor bed and then exposed to optical radiation at the indicated wavelength, leading to tissue destruction; this procedure is still in the experimental phase but with results. The irradiation source used to excite the photosensitiser (Photofrin II) in these cases is a continuous emission laser. This technique is proving very effective in the treatment of recurrent urothelial carcinomas.

Complementary therapy

Conventional, classical treatment of bladder cancer may be combined with complementary treatment including:

- Acupuncture - technique with origins in the Far East (Chinese medicine)
- Phytotherapy (use of products extracted from plants)
- Meditation and yoga (requires the use of relaxation techniques)
- Biofeedback
- Nutritional plans based on specific food combinations, diets.

Complementary therapy will never replace the standard therapy used in bladder tumours.

This combination of complementary therapies should always be carried out after prior discussion with the treating physician, who will of course always weigh the risks and benefits of these therapies.

Patients also ask to be included in clinical trials that will practically follow the risk/benefit ratio of the combination of complementary therapies in the management of urothelial tumour pathology.

This inclusion in clinical trials will be done in compliance with certain criteria established in advance by the clinician with the written consent of the patient, who may at any time withdraw from these trials. The purpose of these clinical trials is to study and determine the optimal treatment for this pathology.

Prophylaxis

Preventing bladder cancer involves taking a number of steps to reduce the risk factors involved in developing the condition. Quitting smoking and avoiding exposure to cigarette smoke are essential steps, as smoking is directly associated with an increased risk of bladder cancer. At the same time, limiting exposure to harmful chemicals such as unsaturated polycyclic hydrocarbons can help protect bladder health.

Arsenic, a substance present in some water sources, can be a risk factor, so it is recommended to use tested drinking water and bottled water to minimise exposure. Adopting a balanced diet, based on low-fat foods and rich in fruit, vegetables and plant proteins, can be beneficial in reducing the risk of bladder cancer. Adequate fluid intake is also crucial for diluting chemicals in the body.

Supplementing the diet with essential vitamins such as A and C can strengthen the immune system and provide possible protection against bladder cancer. It is important to pay attention to the quality of water consumed and to avoid dehydration, as adequate hydration can help eliminate toxic chemicals.

It is also vital to point out that despite prevention efforts, bladder cancer can progress and give rise to secondary determinants such as lymph, bone, liver and lung metastases. Regular health monitoring, especially in patients with a history of bladder cancer, is essential for early detection of possible recurrences or complications.

Survival rate

A better prognosis is found for papillary carcinomas compared to other types of bladder tumours. Patient prognosis also depends on the stage of the disease and locoregional extension, secondary determinants.

In terms of the 5-year survival rate, the following is found:

- In stage 0: a 5-year survival rate of 98%
- In stage 1: a 5-year survival rate of 88 %
- In stage 2: a 5-year survival rate of 66%
- In stage 3: a 5-year survival rate of 46%
- In stage 4: a 5-year survival rate of 14-15%. [2]

These survival rates refer to all types of urothelial tumours, not just papillary tumours.

These figures are general estimates, reflecting the average survival rate for certain time periods after diagnosis.

These estimates cannot provide an accurate prediction of the individual course of the disease for each patient.

Prognosis:

The prognosis for prostate cancer can vary significantly and depends on several factors, including stage at diagnosis, histological grade of the tumour, patient age, presence of other health conditions and response to treatment. It is important to note that prognosis is an estimate of the likely course of the disease, and each case is unique.

In general, most prostate cancers are diagnosed in the early stages, when the tumour is located inside the prostate. In such cases, the prognosis is often favourable and the chances of cure are high. Treatments for prostate cancer may include prostatectomy (removal of the prostate), radiotherapy, hormone therapy or active surveillance, depending on the specifics of each case. In cases where prostate cancer has spread outside the prostate or metastasised to other parts of the body, the prognosis may be more guarded. However, current treatments, including hormone therapy, chemotherapy and other options, can help control the disease and relieve symptoms.

CHAPTER II Personal side

Material and working method

All the above aspects will be followed up on an appreciable number of cases in a prospective and retrospective study that will allow conclusions to be drawn, thus making it possible to compare them with existing data in the literature and in specialised protocols.

Description of batches:

Batch A - patients diagnosed with tumors limited only to the bladder

Batch B - patients with bladder tumours associating pelvic secondary determinations

Patients from both batches will be analysed and followed up:

- The presence of risk factors in both batch A and batch B
- The presence of secondary determinations and the most frequently identified sites
- Means of treatment used and post-treatment evolution, determination of the most effective treatment regimens.
- Determination of the most aggressive histopathological forms of bladder carcinomas, determination of the forms and their ability to spread.

In this regard, a vital role is played by cystoscopic examination, ultrasound examination, CT examination, MRI examination, and, most importantly, histopathological examination, which will help me establish correlations between the anatomopathological variant and the capacity of infiltration and invasion, both of the bladder and the pelvic organs in the vicinity.

Clinical diagnostic elements, belonging to the family doctor (primary care), which have predictability for the prognosis of the development of bladder cancer, as well as the paraclinical signs exploitable in early forms, will be analysed. I will analyse a sample of information: clinical, paraclinical, markers, neoplastic familial charge, which I will transform into a guide for early diagnosis of bladder cancers, avoiding the pelvic invasion phase as much as possible.

Study inclusion criteria

Patients included in the study will be selected according to certain criteria such as: gender, presence of bladder tumors in the history, alcohol /tobacco consumption, presence of other associated diseases /comorbidities (AMI, hypertension, obesity, diabetes mellitus, dyslipidemia, UTI).

The data required for the study will be taken from the clinical observation sheets of the Urology Clinic of "Sf. Apostol Andrei" Emergency Hospital in Constanta.

Patients will be investigated both preoperatively and postoperatively, in evolution.

In other words, the parameters that I will be tracking, I intend to include in a template sheet, to facilitate data collection and which I will use like a time monitoring scheme for the data that I will include in it.

Material and method

The retrospective study includes 174 patients from the Urology Clinic of "Sf. Apostol Andrei" Emergency Hospital in Constanta, during the period 2016-2020, where we analyze the main factors leading to the development of urothelial carcinomas. The study involved 174 patients, divided into 2 batches, Batch A and Batch B. Batch A includes patients with anatomopathologically confirmed diagnosis of bladder carcinoma, while in Batch B are patients without diagnosis of bladder carcinomas.

We will follow the treatment of patients in the Urology Clinic of "Sf. Apostol Andrei" Emergency Hospital in Constanta in the period 2016-2020.

I would like to mention that the year 2020 was a turning point year in which the SARS-Cov 2 Pandemic drastically decreased the number of patients, who could no longer benefit from optimal treatment, specialist control, an aspect that is reflected in the number of severe cases that came post Pandemic.

The study involved 174 patients, 107 in Batch A, 67 in Batch B, categorised as shown in Figure 1:

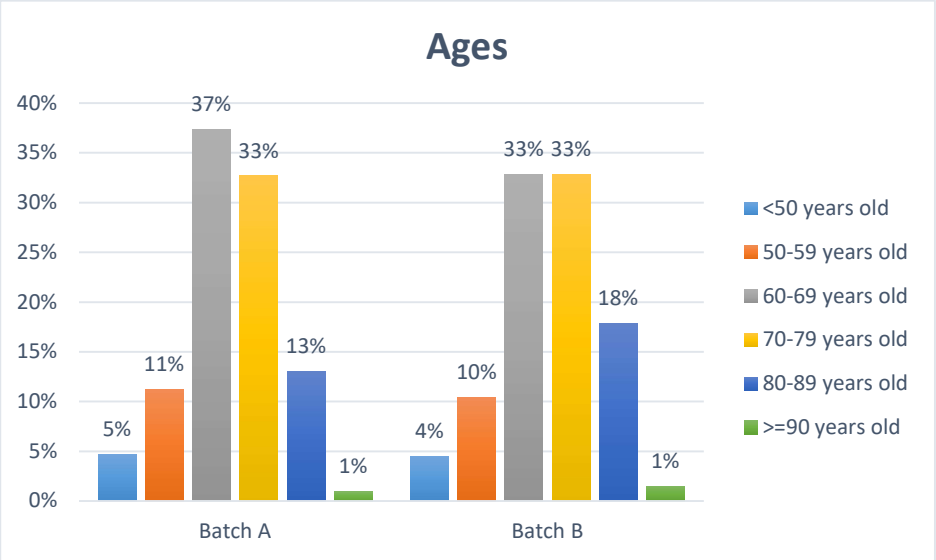


Figure 1 Share of patients by age

In Batch A, the largest share is in the 60-69 age group, 37%, followed by the next age group, 70-79, 33%. The same is true for Batch B where both age groups have equal shares, 33%.

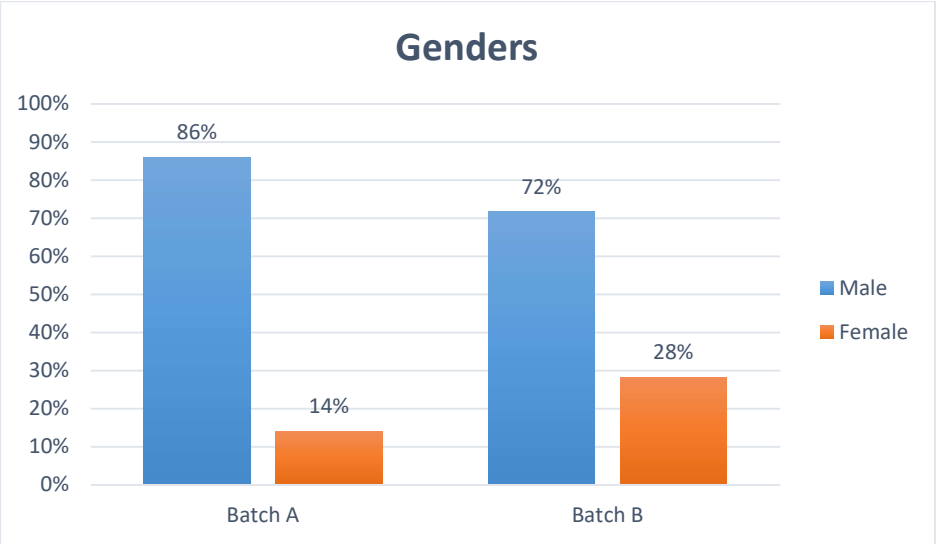


Figure 2 Distribution by gender

In terms of patient gender, the percentages obtained were (as can be seen in Figure 2):

- There are 92 males (86%) and only 15 females (14%) in Batch A.
- There are 48 males (72%) and 19 females (28%) in Batch B.

There is a higher proportion of males than females, which may be related to higher tobacco consumption and interaction with occupational factors such as polycyclic hydrocarbons from the oil industry, plastics, solvents, paints, pesticides.

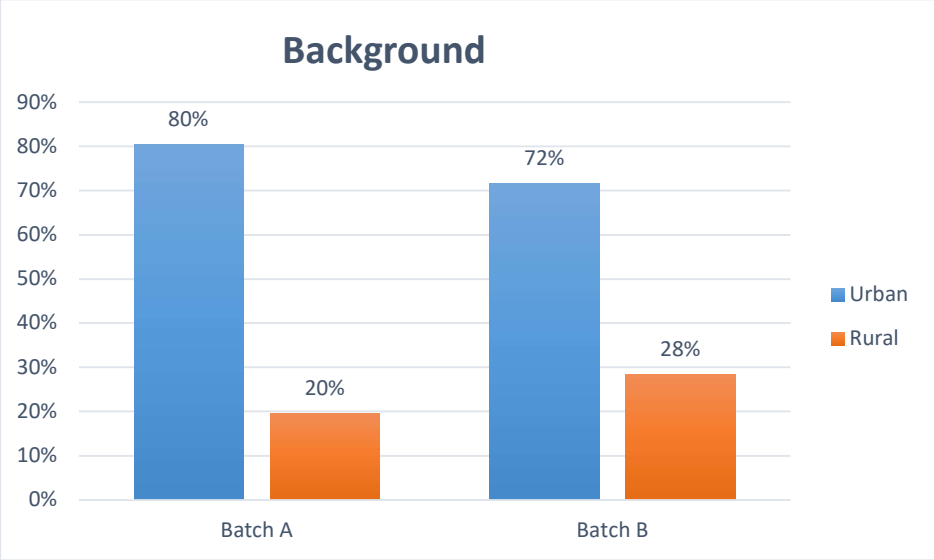


Figure 3 Distribution of patients according to their background

Figure 3 shows the background of the patients, with the highest proportion in Batch A in urban areas with 86 patients (80%), higher than in rural areas where only 21 patients (20%) were identified. In Batch B, the proportions are similar, 48 patients in urban areas (72%) and 19 in rural areas (28%). The high proportion in urban areas is also due to the easy access to specialised medical services, the higher level of education and the higher financial possibilities in urban areas.

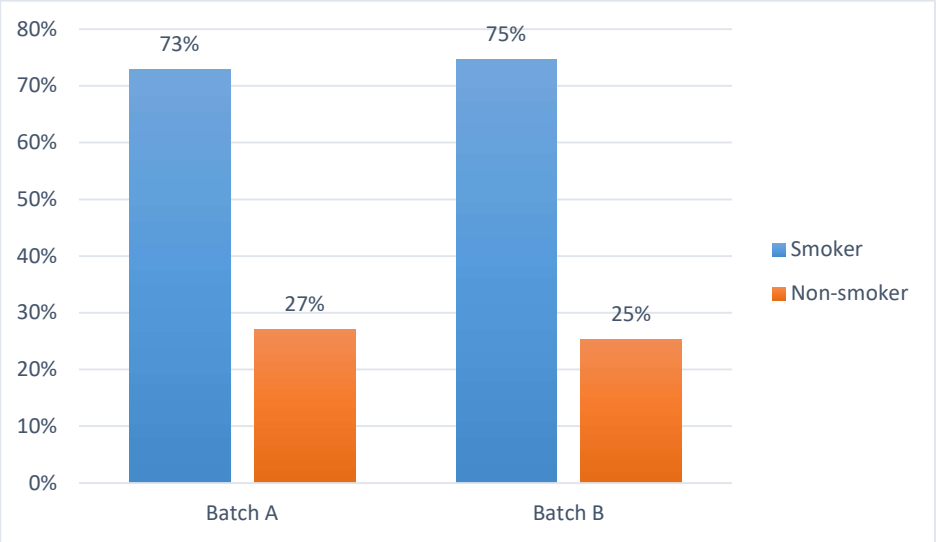


Figure 4 Share of smoking and non-smoking patients

Of the patients participating in the study, in Batch A 78 of them (73%) declared themselves smokers and 29 (27%) were non-smokers, as shown in Figure 4. In Batch B there are 50 smokers (75%) and the remaining 17 are non-smokers (25%).

In this situation, the influence of direct proportional smoking as a major predisposing factor in the development of bladder carcinomas, due to chemical products (hydrocarbons) resulting from tobacco burning, can be clearly observed.

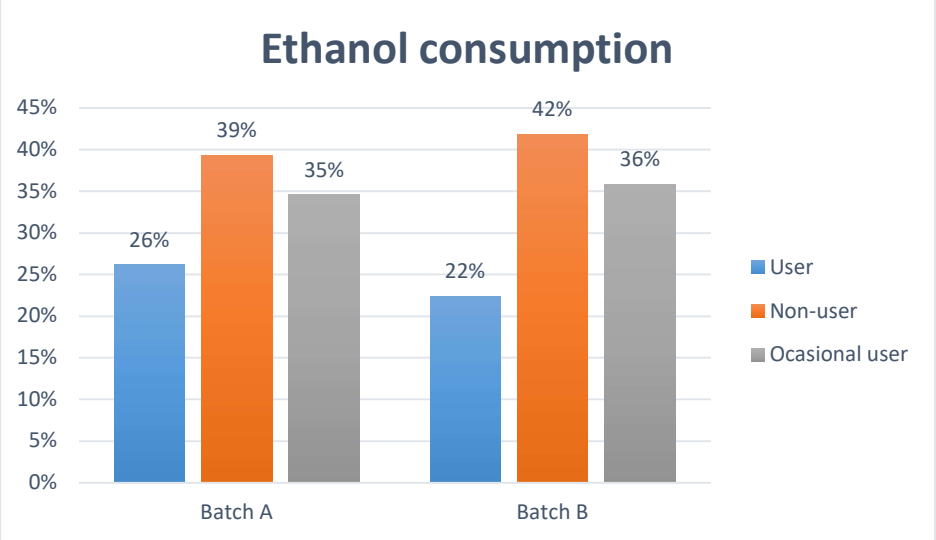


Figure 5 Distribution by ethanol consumption

The proportion of patients affected by ethanol consumption is shown in the graph in Figure 5 where 42 patients (39%) declare themselves non-users, having the highest proportion. In Batch B, their share is even higher, 42%, 28 patients. There are 37 people who declare occasional consumption (35%) and 28 declare themselves to be consumers (26%) in batch A. In batch B there are 24 occasional consumers and 15 declare themselves to be consumers (22%).
Ethanol consumption is a predisposing factor, but a small proportion of study participants report using ethanol, we have no information on the amount of ethanol consumed daily.

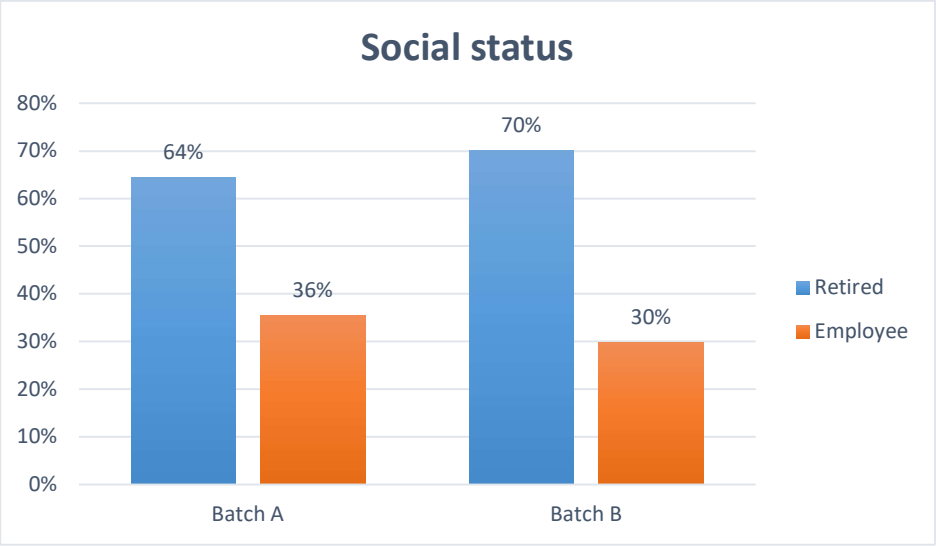


Figure 6 Social status of patients

The social status of the patients (Figure 6) was divided between employed and retired, of which only 38 are employed (36%) and 69 are retired (64%) in Batch A. For those in Batch B, also most are retired, 47 patients (70%), the other 20 patients are employed (30%).
Since this pathology occurs mainly after the age of 60, there is a higher incidence among retired people.

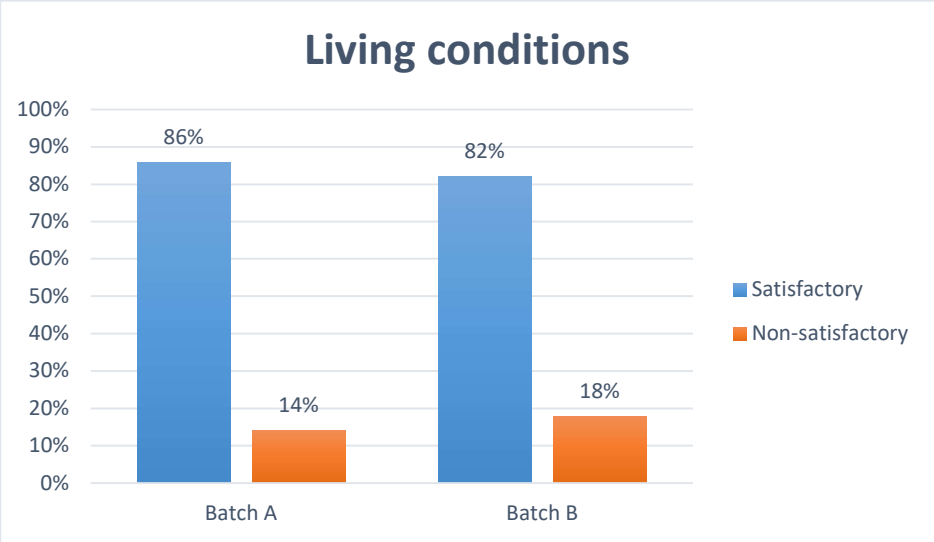


Figure 7 Share of patients by living conditions

Patients' living conditions was a criterion of investigation in the present study, and Figure 7 shows that in Batch A the highest proportion is 92 patients (86%) who declare to have satisfactory living conditions and only 15 of them (14%) declare to be dissatisfied with their living conditions. In Batch B, 55 patients declare satisfactory living conditions (82%) and 12 of them are dissatisfied with their living conditions (18%).

The majority of patients included in the study report satisfactory living conditions, being satisfied with their living conditions, a small proportion being dissatisfied with their living conditions.

Patients who are dissatisfied with their living conditions are usually from rural areas and do not have easy access to specialised medical services. In the literature and in other studies, we can see that there are not many studies showing the link between living conditions and the incidence of bladder tumours, but a direct correlation can be made between prognosis and living conditions, with a lower prognosis in those with unsatisfactory living conditions.

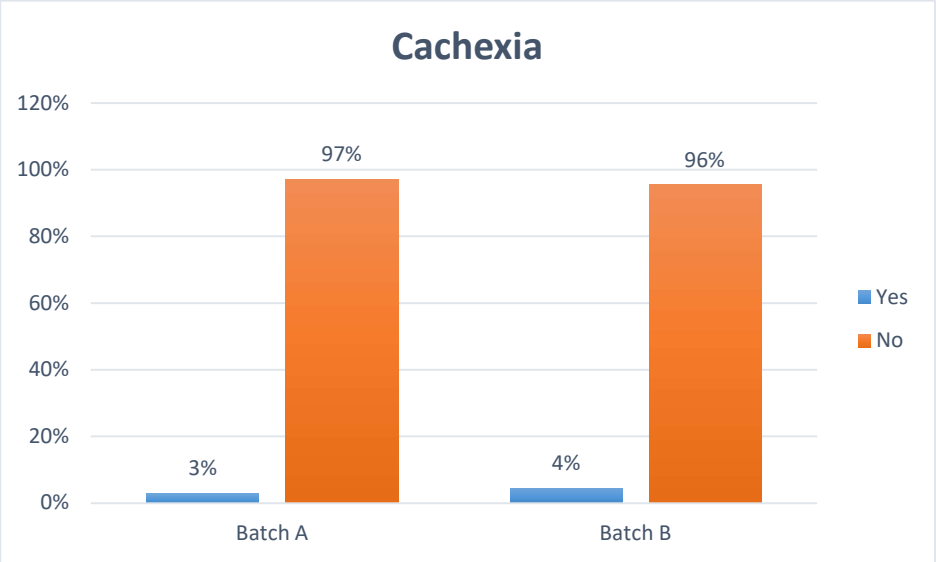


Figure 8 Cachexia share

Denutrition was taken into account in this study, so only 3 people (3%) in Batch A expressed a state of deep weakness (cachexia), while the remaining 104 people, as shown in figure 8, do not suffer from this symptom (97%), which is the highest proportion. In Batch B, things are unchanged: 3 people declare cachexia (4%), 64 do not have this symptom (96%).

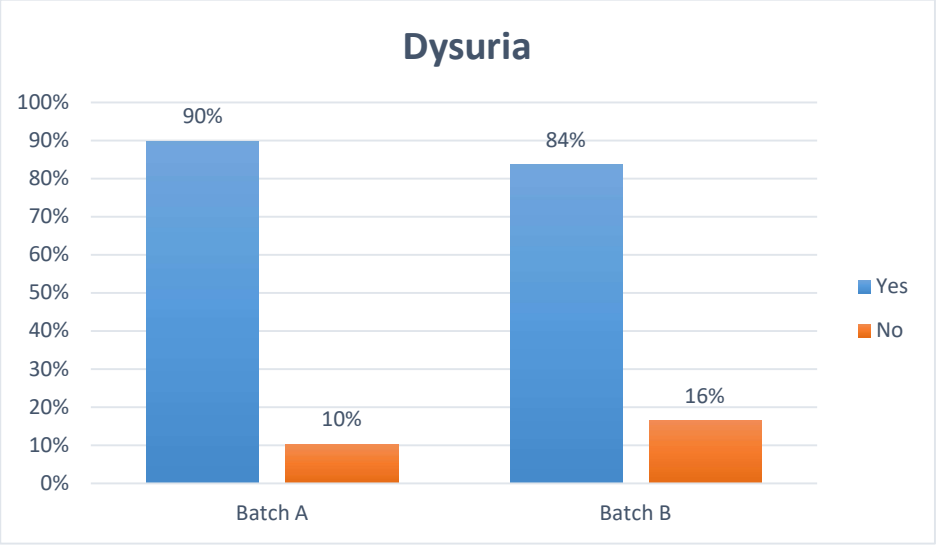


Figure 9 Dysuria share

A significant proportion of patients suffer from dysuria, in Batch A there are 96 people (90%) probably indicating urinary tract infection. Only 11 patients (10%) do not show this symptom. In Batch B there are 56 people with dysuria (84%) and the rest without, 11 (16%).

Dysuria in this situation occurs due either to the coexistence of urinary tract infection whose development is favoured by the patients' deficient immune terrain, or due to tumor invasion.

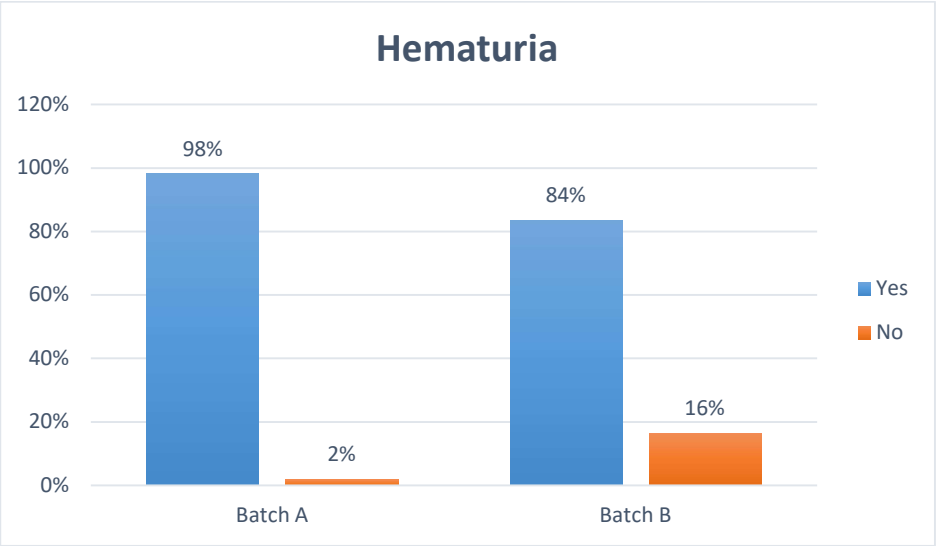


Figure 10 Hematuria share

A very high proportion of patients with hematuria, 105 patients (98%), possibly extraglomerular and only 2% without this diagnosis in Batch A. For Batch B, there are 56 people with hematuria (84%) and a significant 16% are not patients with hematuria.

Hematuria is the most frequently present sign, being the one that alarms the patient and leads him to refer to the Urology Service.

Hematuria is usually associated with clots which also favour the appearance of dysuria and even urinary retention.

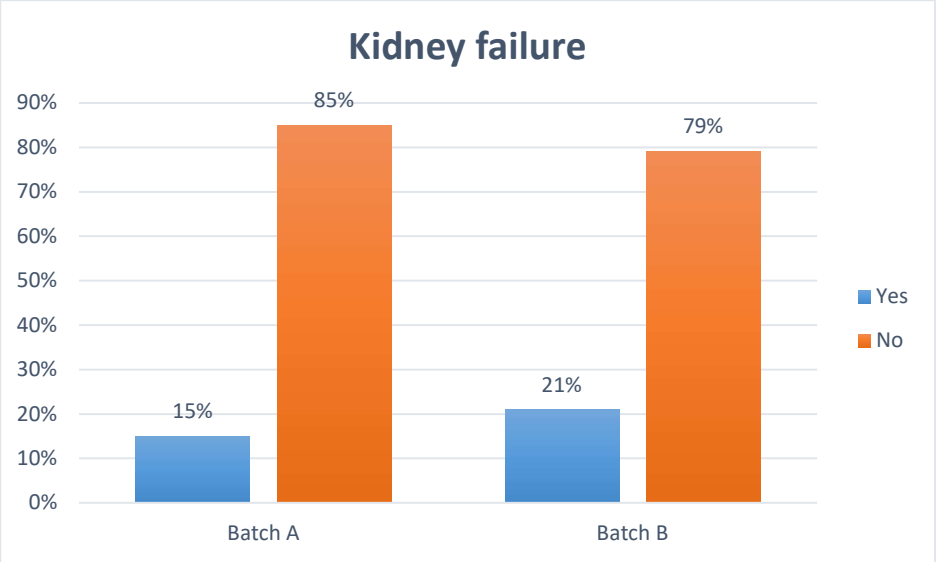


Figure 11 Share of patients with kidney failure

Most patients in Batch A, 91 (85%) report that they do not suffer from this chronic kidney disease. However, 16 of the patients (15%) in this study were diagnosed with kidney failure, as shown in Figure 11. In Batch B, there are 53 patients who do not have kidney failure (79%) and 14 of them suffer from this disease in a significant percentage of 21%.

Kidney failure in this situation is either an associated comorbidity of the patient or occurs due to the extension of the tumor bed, which encompasses the Ureteral Orifices and causes this secondary kidney failure.

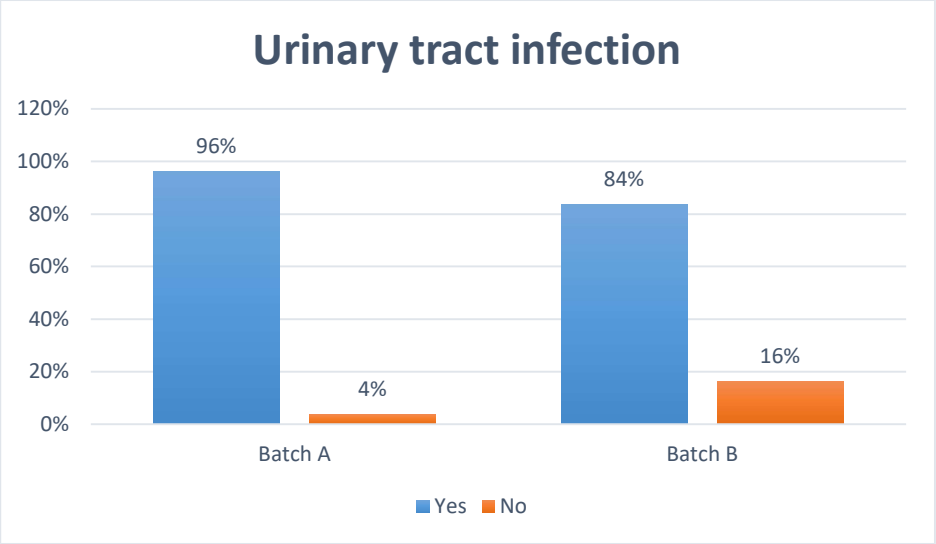


Figure 12 Distribution of urinary tract infection in patients

A majority of the patients included in the study in Batch A reported urinary tract infection, 103 (96%) and only 4 patients do not have this diagnosis of cystitis (4%). In Batch B, 56 patients have this infection (84%) and 11 (16%) do not have this disease.

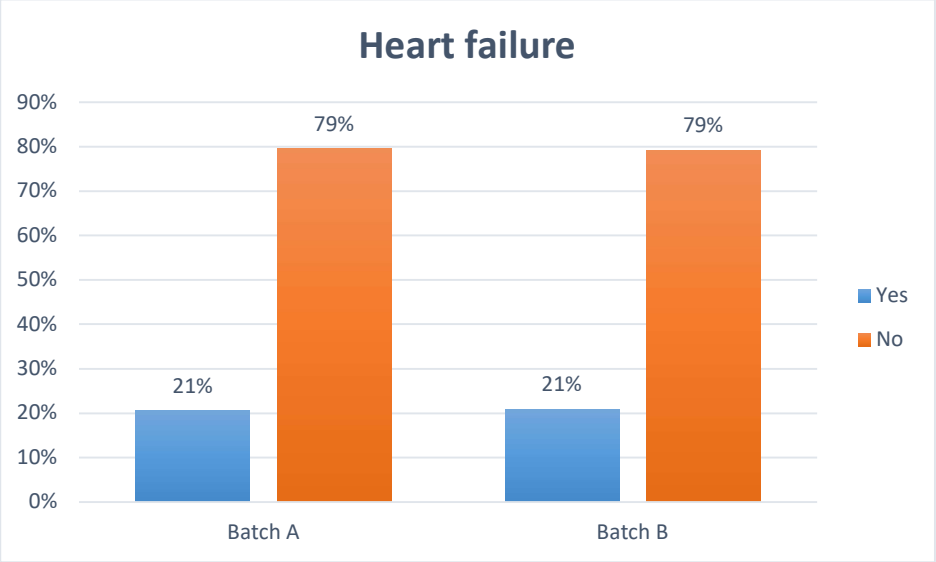


Figure 13 Share of patients with heart failure

Heart failure is a symptom seen in 22 of the patients in this study in Batch A (21%), and further analysis will be needed to identify the causes of heart failure for future therapy. But 85 patients do not have heart failure (79%). In group B, 14 patients have heart failure (21%) and 53 do not (79%).

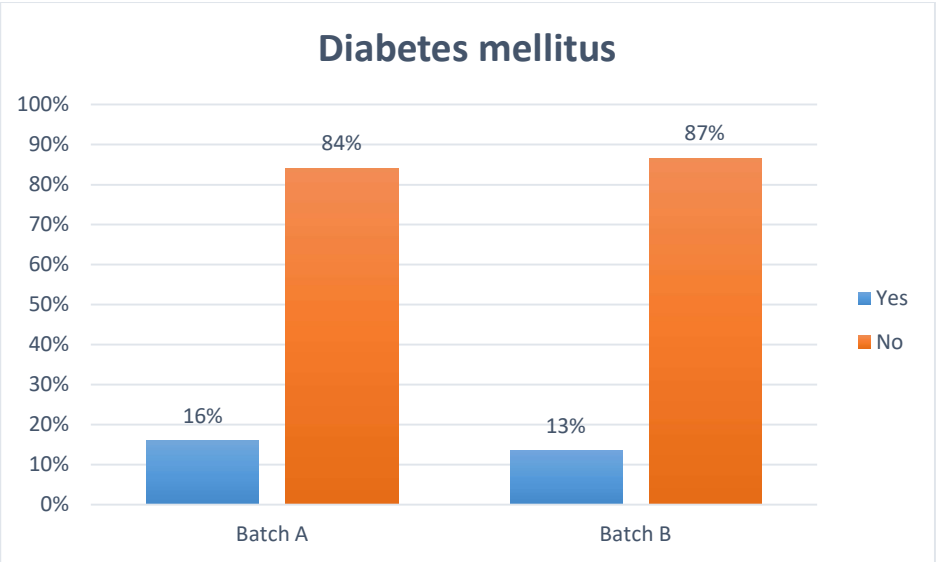


Figure 14 Share of patients with diabetes mellitus

Figure 14 shows that in Batch A, 84% of patients do not have a significant blood glucose concentration (90 patients). Only 16% were diagnosed with this chronic disease (17 patients). For Batch B, 58 patients (87%) do not have diabetes mellitus and 9 people (13%) have this disease.

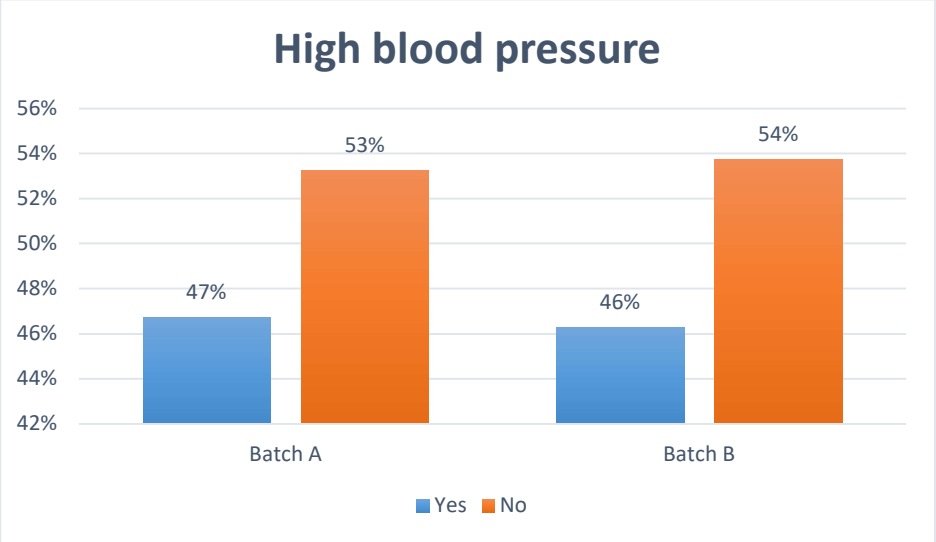


Figure 15 Distribution by hypertension in patients

In the present study there are high proportions of those who present with hypertension and those who do not present with hypertension. 50 patients (47%) were diagnosed with hypertension and will need to be carefully monitored and treated in Batch A. 57 of the patients included in the study do not present with this condition (53%). In Batch B, 31 patients (46%) present with symptoms of hypertension and 36 patients (54%) do not present with these symptoms.

A direct correlation between hypertension and bladder carcinomas cannot be established.

This comorbidity is a specific pathology of the elderly but does not directly influence the development of urothelial carcinomas, it however does influence the risk of surgery.

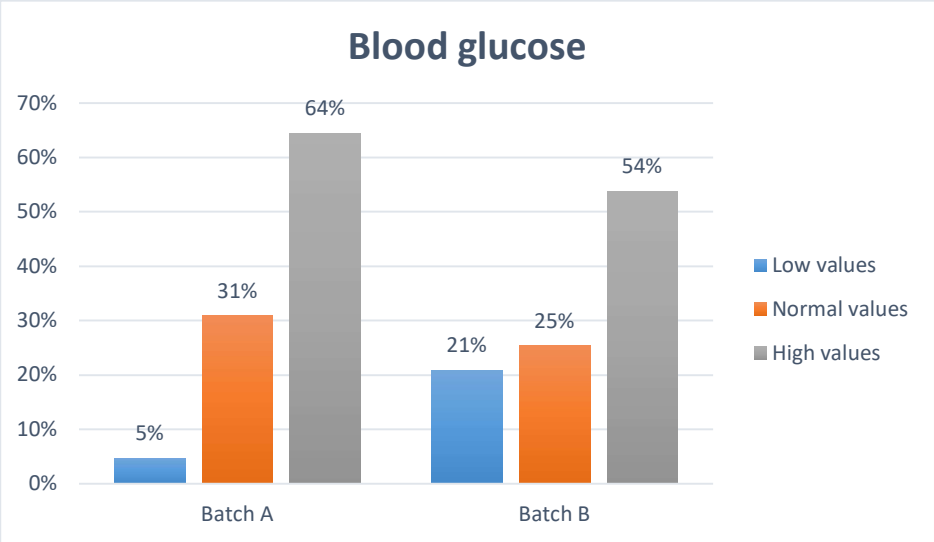


Figure 16 Distribution by blood glucose

Figure 16 for Batch A shows that there are 33 patients with normal blood glucose values (31%). There are also 5 patients (5%) for whom the blood glucose concentration has fallen below 60 mg/dl and below the hypoglycaemic limits. A total of 69 patients (64%) with values above 99 mg/dl with hyperglycaemia were observed during the investigation, thus with the highest proportion. In Batch B, 17 patients had normal values (25%), 14 low values (21%) and the highest proportion of patients had high blood glucose values, 36 patients (54%).

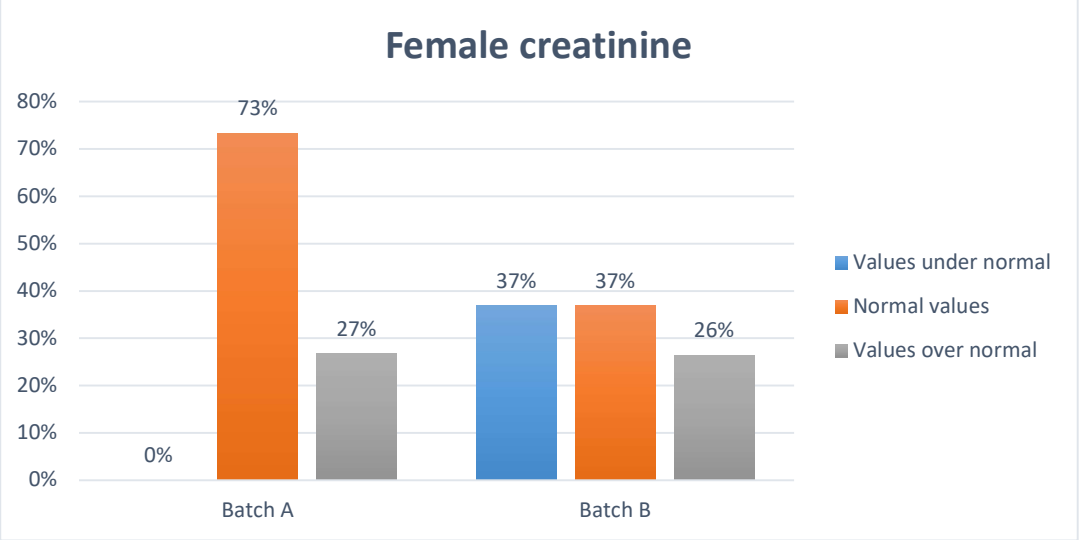


Figure 17 Normal creatinine distribution in females

The most values are normal for the creatinine indicator in women, 11 patients (73%). Below normal values there are no patients in Batch A, and above normal are 4 patients (27%), indicating an impaired glomerular filtration rate. For Batch B, 7 patients have creatinine values below normal (37%), 5 patients have values above normal and 7 have normal creatinine values in women (37%).

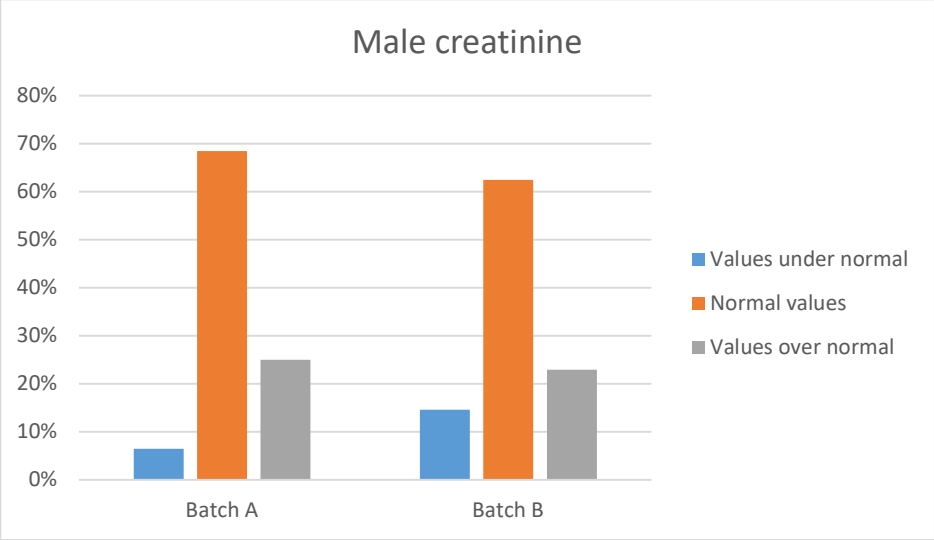


Figure 18 Normal creatinine distribution for males

For the creatinine indicator values in males in Batch A, 63 of the patients have normal creatinine values (68%), representing the highest proportion, 6 of them (7%) have values below normal and 23 patients (25%) have values above normal, also indicating an impaired glomerular filtration rate. For Batch B, the highest proportion is of patients with normal creatinine values, 30 (63%), and 11 (23%) have high values. In this batch, only 7 patients (15%) have lower than normal values for male creatinine.

Creatinine determines the degree of kidney impairment patients have.

Kidney failure can be caused either due to the age of the patients, being kidney failure of renal cause, or due to tumor invasion, or kidney failure of postrenal cause due to tumor invasion trapping the ureteral orifices.

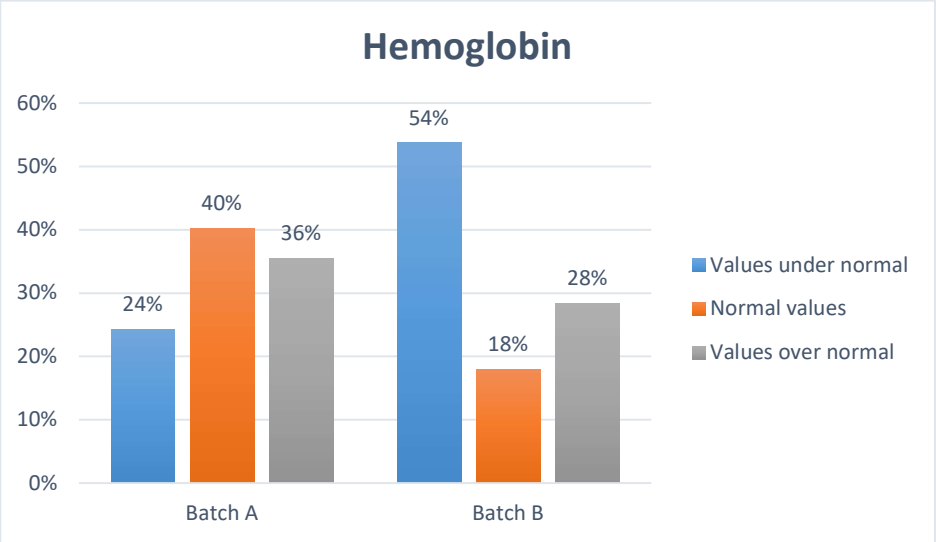


Figure 19 Hemoglobin values share

In the study (Figure 19), in Batch A, 43 of the patients had normal hemoglobin values (40%), with the highest proportion. Below the normal range of this indicator are 26 patients (24%), probably patients with different forms of anemia. A significant proportion of 38 patients (36%) are also patients with above normal hemoglobin values, probably with lung disease, or patients with heart activity below normal parameters. For the hemoglobin values of patients in Batch B, most patients have values below normal in 36 patients (54%). 19 patients have high hemoglobin values (28%) and only 12 have normal hemoglobin values (18%).

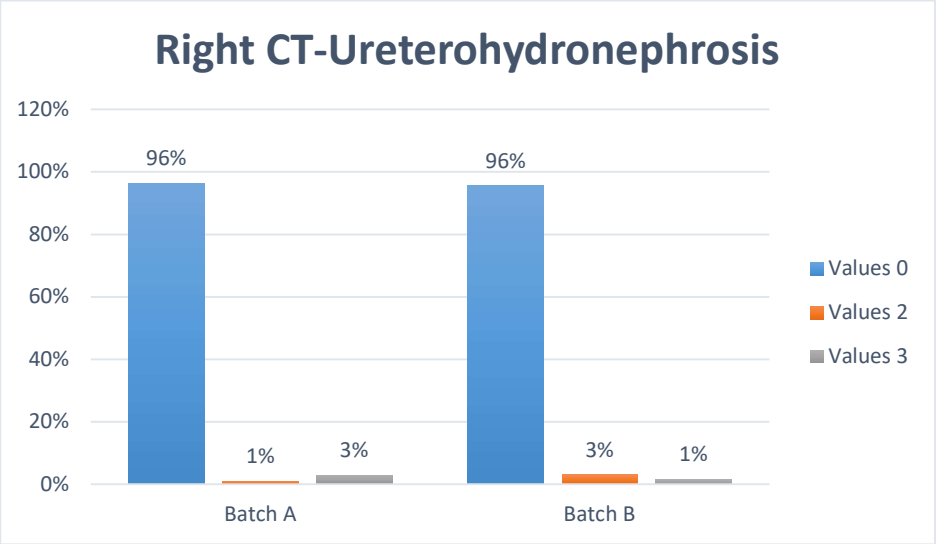


Figure 20 Distribution of CT-Ureterohydronephrosis

Figure 20 shows a majority share of values 0 in 103 patients (96%) in Batch A in terms of right CT- ureterohydronephrosis, while values 2 and 3 have insignificant weights in 1 and 3 patients, respectively. For Batch B, 64 patients show values 0 with the highest weight (96%). Only two patients with values 2 and one with values 3.

Ureterohydronephrosis is given by tumour invasion at the ureteral orifices.

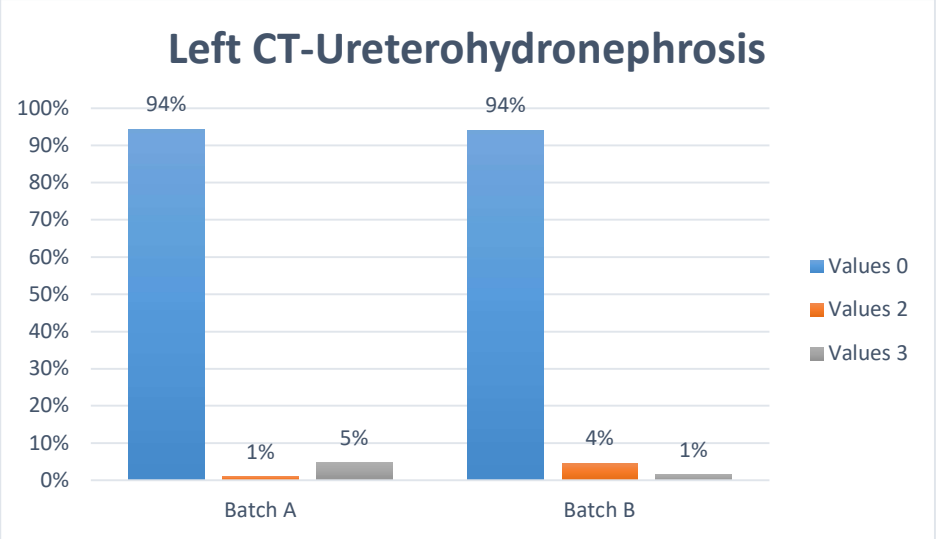


Figure 21 Distribution of left CT-Ureterohydronephrosis

For the indicator left CT-Ureterohydronephrosis, the majority percentage is for the value 0, encountered in 101 patients (94%). For values 2 and 3 the distribution is insignificant, values encountered in 1 and 5 patients respectively of Batch A (Figure 22). In Batch B, also the significant share is for patients with values 0, 63 patients (94%). With values 2 and 3 there are only 3 and one patient, respectively.

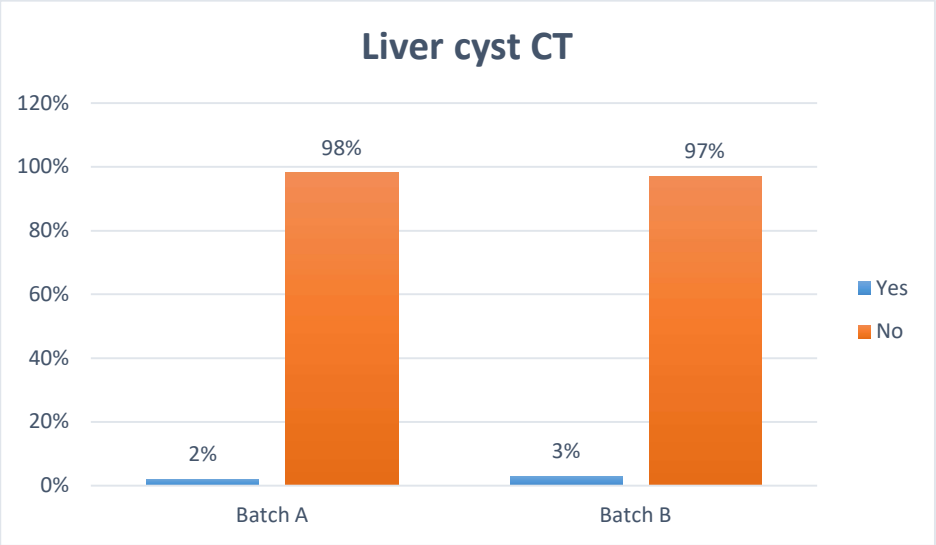


Figure 22 Distribution of liver cyst CT

In the present study in Figure 22 it is observed that only 2 out of the total patients have liver cyst (2%), the remaining 105 patients have no liver cyst in a majority proportion (98%). In group B, 65 patients have no liver cyst in a majority proportion of 97%. Only 2 patients have liver cyst.

Liver cyst in this case is discovered by accident, is not a determining factor in bladder tumor pathology and in no way influences their subsequent therapeutic management.

Simple hepatic cysts do not require surgical sanction, in this study they are only mentioned as incidentals, their presence or absence does not influence the present study.

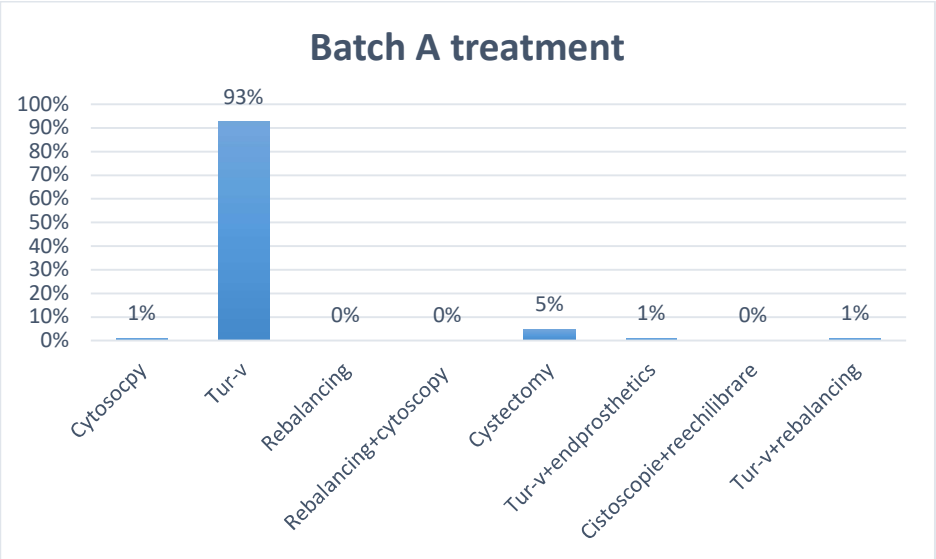


Figure 23 Distribution of treatments used in Batch A

As can be seen from the distribution of patient treatments in Figure 23, for Batch A, the highest proportion is transurethral resection of bladder tumours in 99 patients, which represents a proportion of 93% of all patients. There are 5 patients with cystectomy (5%).

As written in the literature per primam, transurethral, edoscopic means of resection are used.

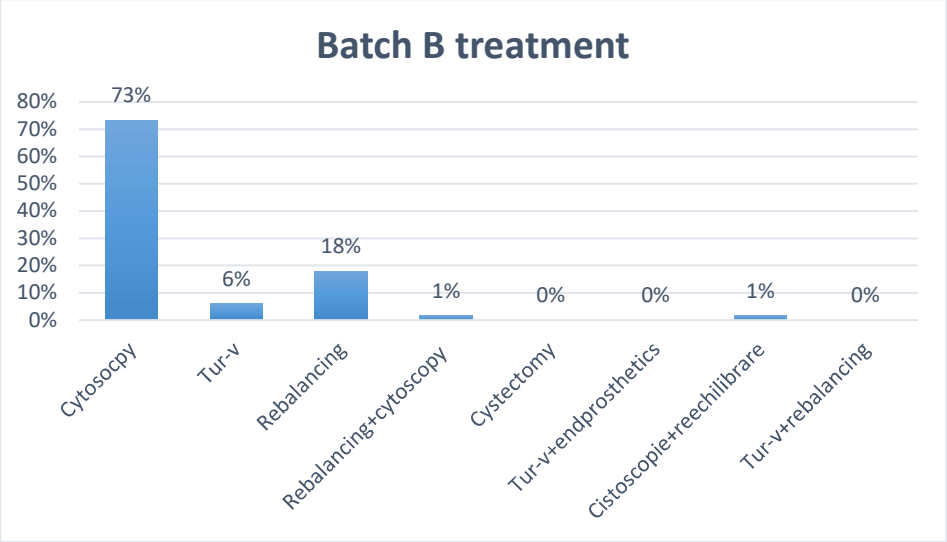


Figure 24 Distribution of treatments used in Batch B

In Batch B (Figure 24), the majority of 49 patients had cystoscopic treatment (73%). Only 4 patients had transurethral resection treatment (6%).

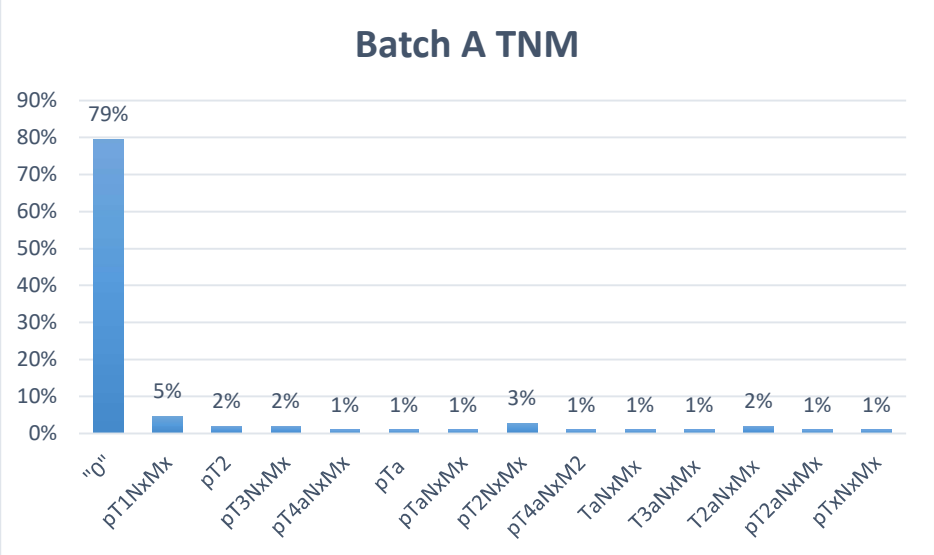


Figure 25 Distribution according to Batch A TNM

Figure 25 shows the characterisation of the degree of locoregional extension of neoplastic disease, 79% of patients in Batch A do not have this characterisation (85 patients). There were 5%, 5 patients with a diagnosis of Pt1NxMx medullary carcinoma.

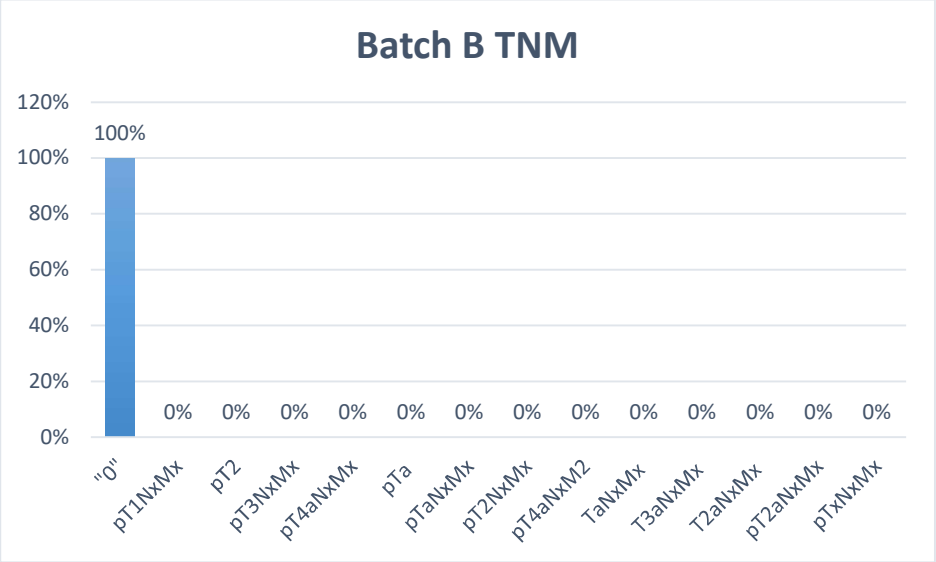


Figure 26 Distribution according to Batch B TNM

For Batch B, 66 patients show a majority of patients with no TNM (Figure 26).

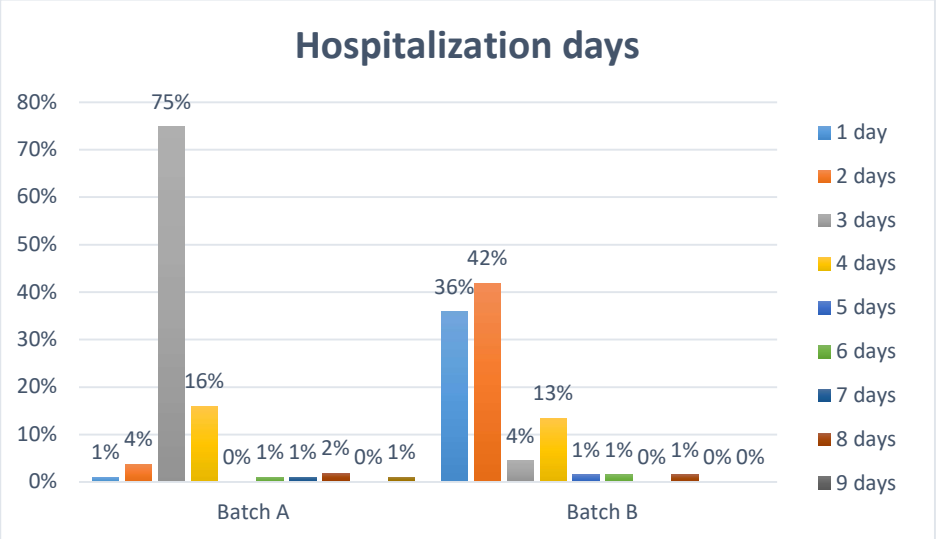


Figure 27 Share of hospitalisation days

Figure 27 shows the distribution of days of hospitalization, which shows a majority share for 80 of the patients admitted for 3 days (75%) for Batch A. Significant shares are also for patients

admitted for 4 days, 17 patients (16%). For Batch B, the highest share is for patients admitted for 2 days, 28 patients (42%), but also for those admitted for 1 day, 24 patients (36%).

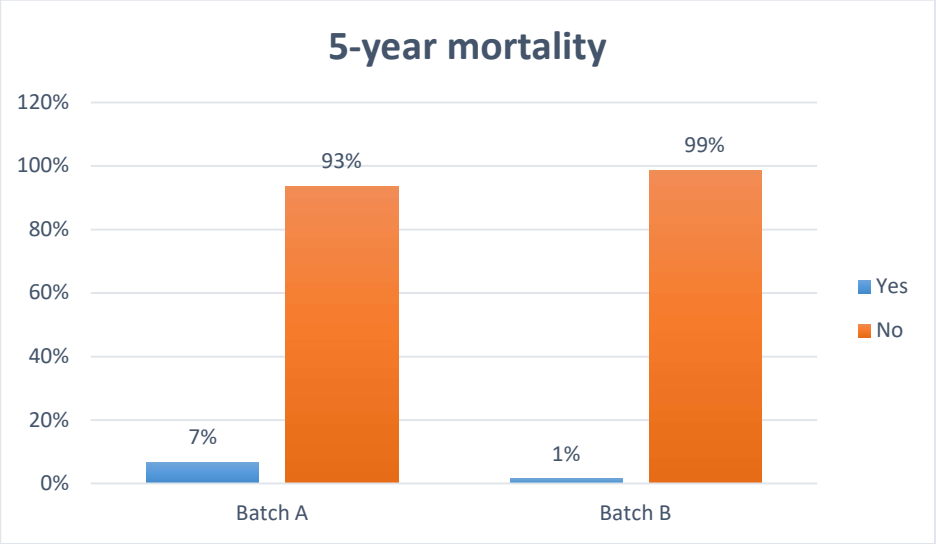


Figure 28 Distribution by 5-year mortality of patients

For the distribution of 5-year mortality of patients, the majority of patients is observed in 100 patients of Batch A who do not qualify for validation of this indicator (93%). Only 7 patients (7%) have 5-year mortality. Figure 28 shows that 66 patients (99%) also do not show validation of this indicator in Batch B.

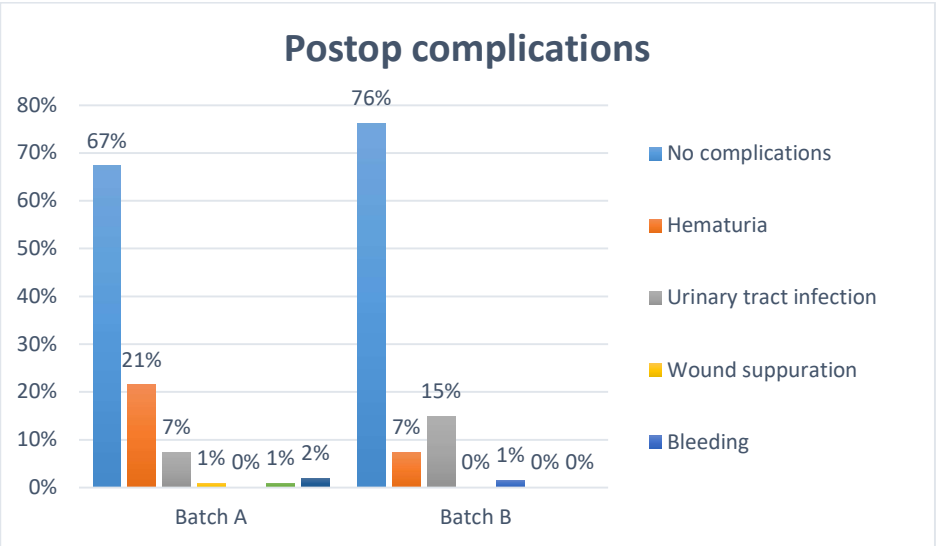


Figure 29 Percentage of post-operative complications occurred

Most patients had no postop complications in Batch A, 72 (67%). 23 patients (21%) of the study group had subsequent blood in the urine (hematuria), and 7% of all patients (8 patients) had urinary tract infection, complications that also occurred postop. In Batch B there are 51 patients (76%) with no postop complications with the highest proportion. 10 patients (15%) presented urinary tract infection and only 5 patients (7%) presented haematuria.

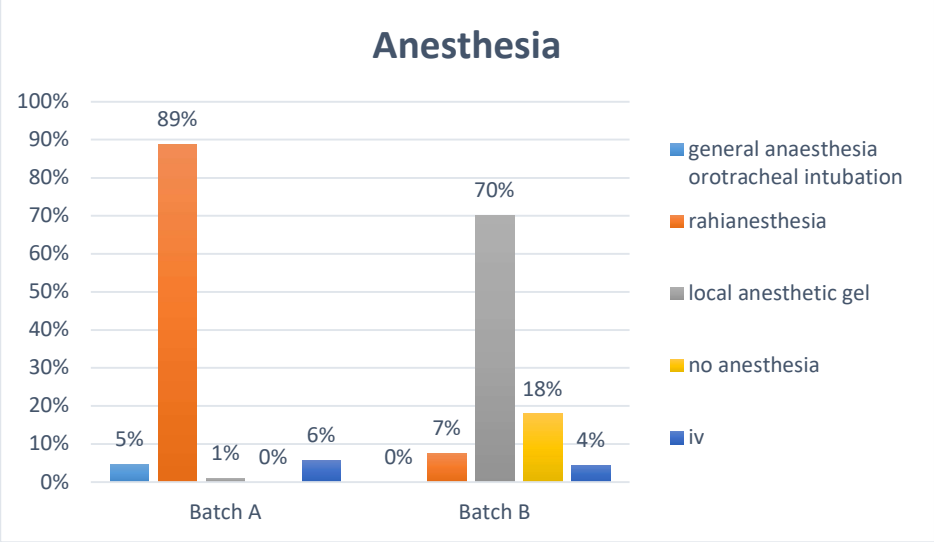


Figure 30 Distribution of patients by anesthesia used

The highest proportion of the total patients in Batch A (89%) is represented by 95 patients who used spinal anesthesia. Also in this batch, 6 patients used intravenous anesthesia. Majoritary is also the share of 47 patients for whom local anesthesia with anesthetic gel was used (70%) in Batch B. 12 patients in this group had no anesthesia, 5 had spinal anesthesia and 3 patients had intravenous anesthesia.

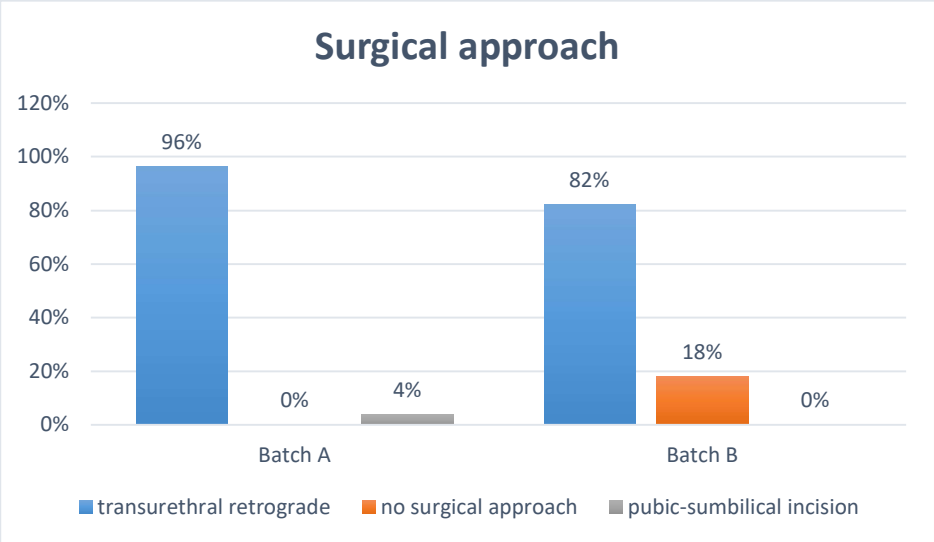


Figure 31 Distribution of patients by surgical approach

Figure 31 shows that in Batch A in the majority of surgical approaches the transurethral bladder resection was used for 103 patients (96%) and pubosumbumbilical incision was used for 4% of patients. In Batch B, the majority share is also for transurethral resection used for 55 patients (82%). For 12 patients in this batch no surgical approach was used (18%).

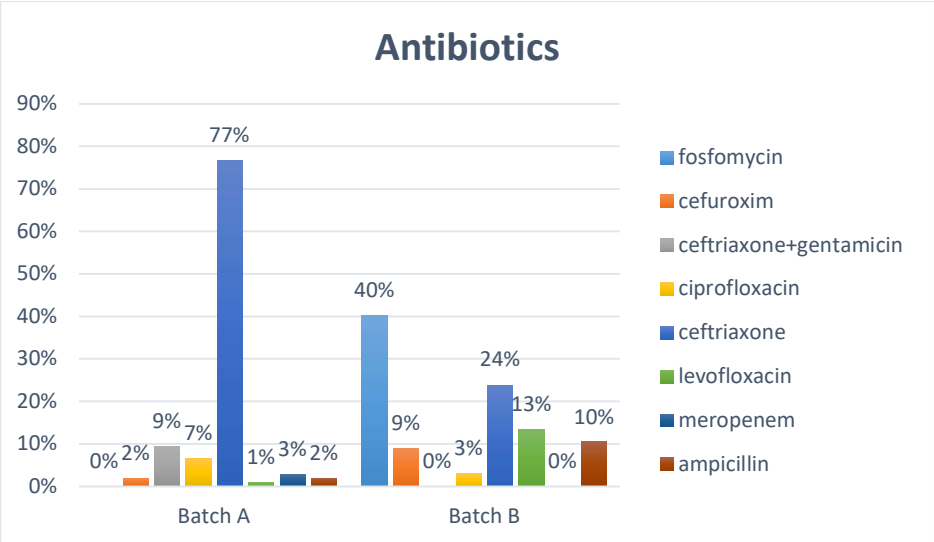


Figure 32 Distribution by antibiotics used

In terms of antibiotic use, the top antibiotic in group A is a cephalosporin antibiotic, ceftriaxone, used by 82 patients (77%), as shown in Figure 32. Figure 32 also shows that 10 patients used ceftriaxone+gentamicin (9%). And in Batch B, for acute, uncomplicated urinary tract infections, 27 patients (40%) used fosfomycin in the majority. 16 patients (24%) used ceftriaxone.

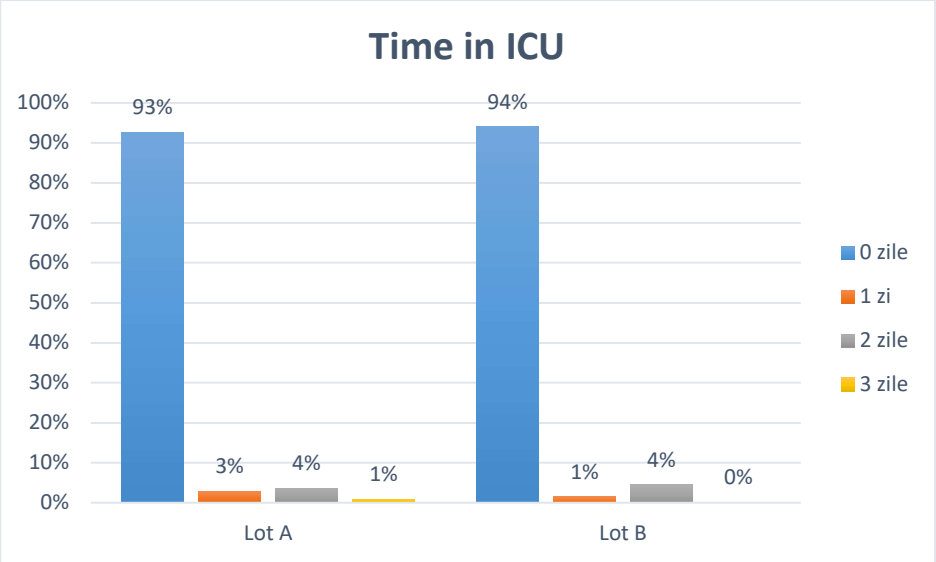


Figura 33 Time in ICU

In terms of time spent in the ICU, the graph in Figure 33 shows that 93% of all patients in Batch A did not stay in the ICU (99 patients). The shares of those who stayed between 1 day and 3 days in the ICU are insignificant. In Batch B there are 63 patients who did not stay in the ICU (94%). Patients undergoing radical cystectomy require 2-4 days of hospitalisation in this service.

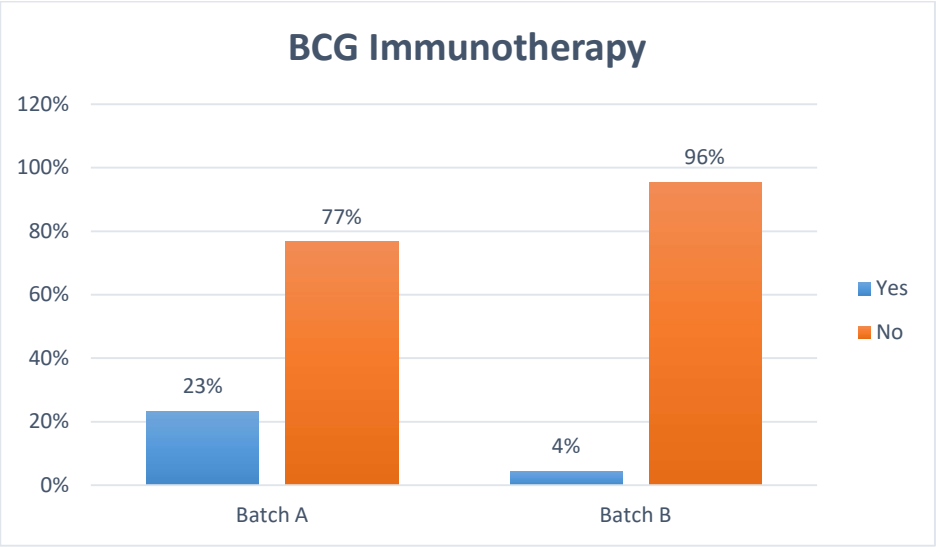


Figure 34 Distribution according to BCG immunotherapy

Treatment with BCG immunotherapy significantly reduces the risk of recurrence of non-invasive bladder tumors. Batch A in Figure 35 shows that 82 patients (77%) did not need this therapy, but

25 patients (23%) (patients with intermediate risk tumors) used topical BCG immunotherapy. In Batch B, the majority of 64 patients (96%) did not need BCG immunotherapy.

The high values of those who did not use BCG are also due to the lack of the product on the Romanian market, patients being forced to purchase it from other EU countries or countries outside the EU.

BCG is the treatment of choice for patients with intermediate- and high-risk bladder tumors, and in these patients BCG has been shown to reduce progression and increase survival rates overall. To understand the mechanism of action of BCG, we can state with the data we have so far, that it is a complex immune mechanism between immune system elements, T lymphocytes and cancer cells. As we elucidate the mechanism of action of BCG and understand the factors that determine it, the immune response will continue to improve.

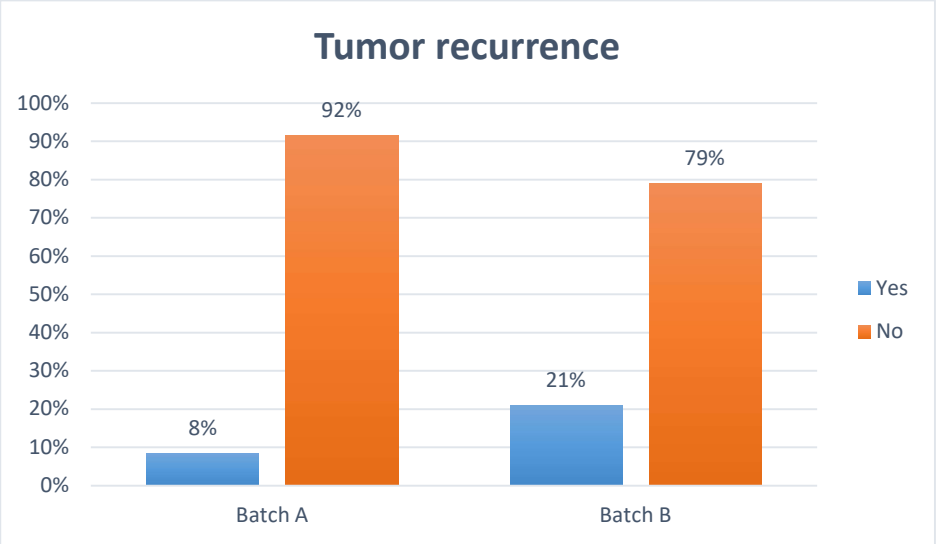


Figure 35 Tumor recurrence occurred

Figure 35 shows that in Batch A only 8% of all patients had relapses (9 patients). The highest share is shown by the remaining 92% who did not show any tumour recurrence. In Batch B, the

highest share of 53 patients did not have recurrences (79%). 21% (14 patients) had tumour recurrences in Batch B.

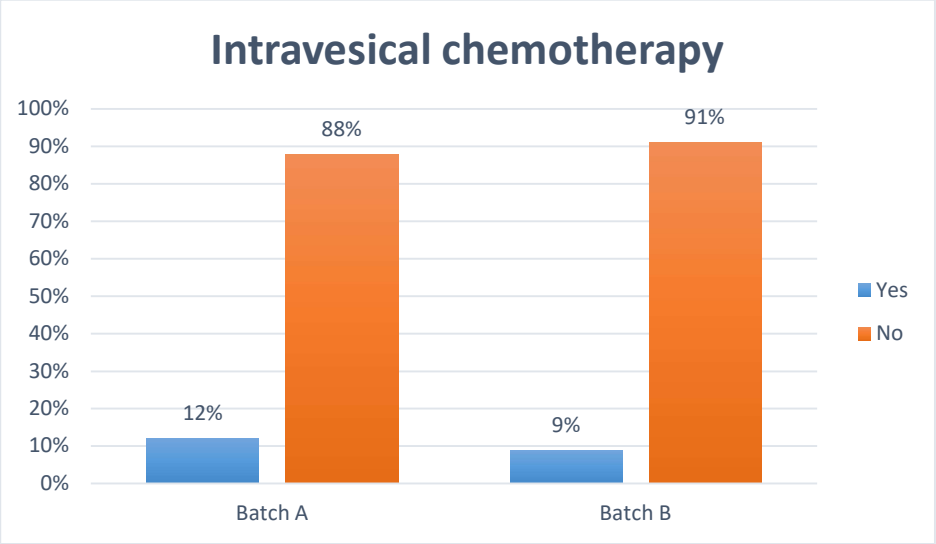


Figure 36 Distribution by intravesical chemotherapy

To reduce the risk of bladder tumor recurrence, 13 patients (12%) used intravesical chemotherapy treatment in Batch A. The remaining 94 patients (88%) did not use this treatment, the highest share. In Batch B, only 6 patients used chemotherapy (9%), but the highest proportion of 91% did not use this treatment as shown in figure 36.

The most commonly used preparations for intravesical istilation are:

- **Mitomycin C** is a chemotherapeutic that stops DNA function at the cellular level, it is a drug easily absorbed through the bladder mucosa.
- Bacillus Calmette-Guerin (BCG) is an immunotherapy for the treatment of bladder tumors that triggers an immune response from the body in the fight against this pathology. Around 60-68% of patients with non-musculoinvasive bladder tumours have a very good response to BCG.

Chemotherapy uses chemical agents that interfere with replication and other intracellular processes that cause the death of potentially tumour-causing cells. Studies in the United States show that using two or more chemotherapeutic agents together has a much better effect than using a single chemotherapeutic agent alone.

Conclusions

1/Tumors with bladder as the starting point, on the group of 174 cases analysed in this research, currently have very good clinical and paraclinical diagnostic chances, including through known tumor markers, but especially with widely applied imaging and acceptance of the fundamental role of cystoscopy.

2/Both for high-grade and low-grade urothelial carcinomas, for transitional (majority) urothelial carcinomas, diagnosis and staging is very accurate and done at an early stage.

3/Cystoscopy has a bivalent role, diagnostic and therapeutic and should be widely used, even if CT, MRI, or Ultrasound imaging are considered very valuable. The gold standard must remain cystoscopy.

4/Comorbidities in old age, when these bladder-onset tumors occur, according to our data, are not insurmountable, as the percentage of patients undergoing laborious operations is not high.

5/These tumours benefit from a therapy somewhat particular to them, through therapeutic agents placed directly on the tumors, with spectacular effects. Here we must remember the modern ones, PD1, PR-L1, which have revolutionized the prognosis in the literature, even in advanced tumors, but on the group we studied, intravesical chemotherapy with Mitomycin C or BCG, are of exceptional value, because BCG stimulates the immune response and inflammation in the tumor bladder wall, achieving very important beneficial effects.

6/ Discovered early, in early stages, especially with early signs such as hematuria, dysuria, polachyuria, etc, this segment of oncology should be classified as a curable cancer in the very near future.

Discussion of therapeutic protocols

In the thesis, 174 cases with bladder tumors are analysed, on our batch it was found that:

They are specific to patients over 55 years of age, with an average around 70 years of age, male gender being more prone than female gender.

As symptoms, we mention hematuria, dysuria, and as diagmostic method of choice is cystoscopy, followed by CT examination.

As a therapeutic method, TUR-V, followed by partial or total cystectomy, is the preferred method.

Postoperatively, follow-up cystoscopy is recommended at 3 months, 6 months, then annually, in order to prevent tumor recurrence.
Also, the earlier they are diagnosed, the easier their treatment will be, with faster recovery.
According to the new European Association of Urology Guidelines, BCG instillation is preferred over intravenous chemotherapy (Epirubicin, Doxorubicin, Famorubicin).

Purpose of the Work

In this paper I demonstrate how, using modern imaging and therapeutic methods, this pathology becomes curable and controllable.