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FINAL DEGREE PROJECT

USE OF MONOPOLAR VERSUS BIPOLAR TRANSURETHRAL RESECTION IN NON-MUSCLE-INVASIVE BLADDER TUMORS RELATED TO THERMAL ARTIFACT AND RECURRENCE AND PROGRESSION RATES

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1. ABSTRACT

BACKGROUND: Bladder cancer is the 10th most common malignant tumor worldwide. 75% of cases are diagnosed at a non-muscle-invasive stage, 90% being of urothelial origin. The management of non-muscle-invasive bladder tumors is based on transurethral resection and the application of adjuvant intravesical therapy. Their main drawback is that they have a high recurrence rate and may progress to a more advanced stage. It exists two main modalities of transurethral resection: monopolar (gold standard) and bipolar systems. The last one has proven to have significant advantages over monopolar energy, such as reducing the presence of thermal artifact in tissue samples, which may interfere in the pathological diagnosis, the basis for the management of these patients. However, there is still controversy about if this reduction have a significant impact on the histological analysis. The recurrence and progression rates decrease with the intravesical therapy, but there are no consistent studies that have evaluated the impact of using one modality of resection or another on these rates.

OBJETIVE: to demonstrate that the use of bipolar transurethral resection in bladder urothelial carcinomas (non-muscle-invasive) reduce the presence of thermal artifact in tissue samples, allowing a proper pathological diagnosis and, consequently, a decrease in the recurrence and progression rates, in comparison to the use of monopolar systems.

DESIGN: It will be a multicenter, longitudinal, prospective, parallel-group, double-blind, randomized and controlled clinical trial carried out in 4 hospitals of Cataluña.

METHODS: Study subjects will be those newly diagnosed of bladder papillary tumors highly suspicious of urothelial carcinoma. They will be classified in 2 groups (as negative or positive cytology) and these will be randomized in 2 groups of intervention (undergo bipolar or monopolar transurethral resection). The pathologist will analyze the thermal artifact and other parameters. The patients will be classified in 3 risk groups (low, intermediate, and high), treated and followed-up for 1 year to evaluate the percentage of recurrence and progression. The sample size will be about 850 patients and recruitment of patients will last 15 months.

KEY WORDS: non-muscle-invasive bladder cancer; transurethral resection; monopolar and bipolar systems; thermal artifact; recurrence rates; progression rates.

2. ABBREVIATIONS

BC	Bladder Cancer
BCG	Bacillus Calmette-Guérin
bTURB	Bipolar Transurethral Resection of the Bladder
CIS	Carcinoma *In Situ*
CEIC	Clinical Research Ethics Committee
CT	Computed Tomography
EBRT	En Bloc Resection
EORTC	European Organization for Research and Treatment of Cancer
HG	High Grade
ISUP	International Society of Urological Pathology
LG	Low Grade
MRI	Magnetic Resonance Imaging
mTURB	Monopolar Transurethral Resection of the Bladder
NMIBC	Non-Muscle-Invasive Bladder Cancer
PDD	Photodynamic Diagnosis
PUNLMP	Papillary Urothelial Neoplasm of Low Malignant Potential
RMBB	Random Mucosal Biopsies of the Bladder
TA	Thermal Artifact
TNM	Tumor, Node and Metastasis classification
TUR	Transurethral Resection
TURB	Transurethral Resection of the Bladder
TURBT	Transurethral Resection of Bladder Tumor
UICC	Union International Contre le Cancer
US	Ultrasounds

3. FIGURES AND TABLES

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4. INTRODUCTION

4.1 BLADDER CANCER

4.1.1 EPIDEMIOLOGY

Bladder cancer (BC) is the 10th most commonly diagnosed cancer worldwide when both genders are considered, with approximately 573,000 new cases and 213,00 deaths. It is more common in men, for whom it is the 6th most common cancer and the 9th leading cause of cancer death (1).

The *worldwide age-standardized incidence rate* (per 100,000 person/years) is 9.5 for men and 2.4 for women (***Figure 1, 2***); and *in the European Union* is 20 for men and 4.6 for women. Incidence rates in both sexes are highest in Southern Europe (Greece, Spain and Italy), Western Europe (Belgium and the Netherlands), and Northern America, although the highest global rates are in Hungary among women. *Worldwide*, the BC *age-standardized mortality* rate was 3.3 per 100,000 among men vs 0.86 for women (***Figure 3***). (1)(2)

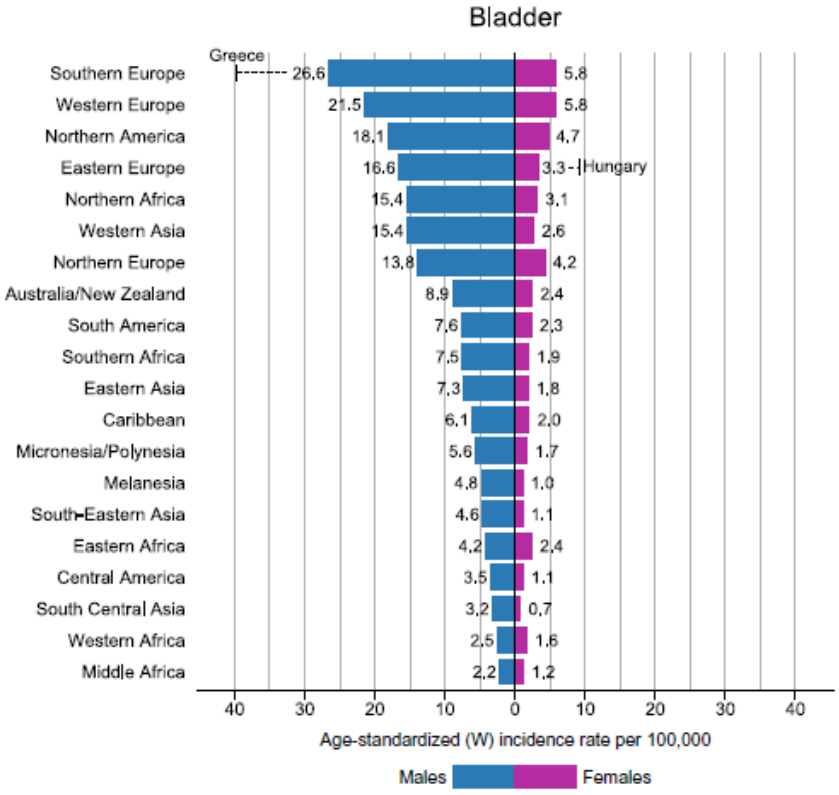


Figure 1. Region-Specific Incidence Age-Standardized Rates by Sex for Bladder Cancer in 2020. Source: GLOBOCAN 2020. (1)

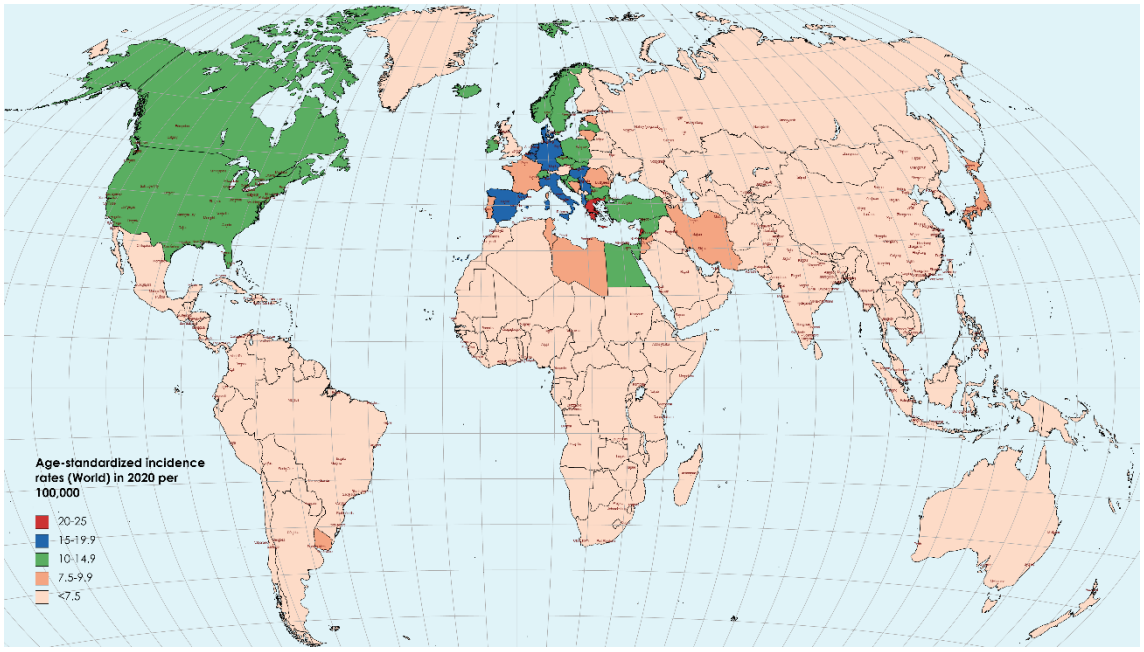


Figure 2. Map showing estimated age-standardized incidence rates for bladder cancer worldwide in 2020, all sexes, including all ages. Created with mapchart.net. Adapted from (3).

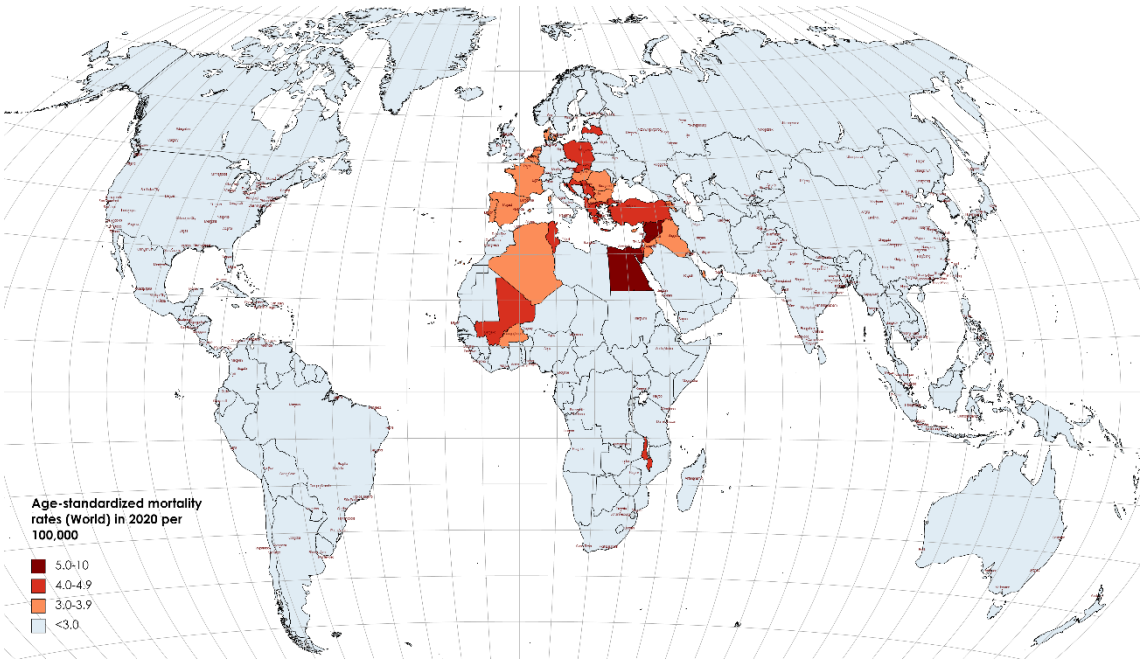


Figure 3. Map showing estimated age-standardized mortality rates for bladder cancer worldwide in 2020, all sexes, all ages. Created with mapchart.net. Adapted from (3).

Bladder cancer incidence is steadily rising worldwide, especially in developed nations, due to the exposure to several polluting agents (3). However, diverging incidence trends were observed by sex in many countries from the 1990s and the early 2010s, with stabilizing or declining rates in men but some increasing trends seen for women (eg, Spain, the Netherlands, Germany, and Belarus). This may be due to the increase in smoking among women since the 1970s, and a decrease in smoking among men recently. In addition, mortality rates have been in decline mainly in the most developed settings due to improvements in early diagnosis and treatment (eg, endoscopic resection, adjuvant instillation of chemotherapy, and intravesical immunotherapy) (1).

The average age of diagnosis is 70 years old (4) and almost 75% of patients debut with "superficial" non-muscle-invasive bladder cancer (NMIBC), that is with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). In younger patients (< 40 years old) this percentage is even higher. Patients with TaT1 and CIS have a high prevalence due to long-term survival and lower risk of cancer-specific mortality compared to T2-T4 tumors (2). Nevertheless, those patients diagnosed with NMIBC have a high risk of recurrence and progression. In general, more than 50% of non-muscle-invasive bladder cancer (BC) affected patients experience recurrence and 10-15% progress to muscle-invasive BC (5), but this varies across the tumor risk category. For instance, low-risk BC (primary, single, Ta G1, <3 cm, without associated CIS) have a recurrence rate between 50-70% and a progression rate of 5% in the following three years of follow-up; however, high-risk category (T1, G3, CIS or multiples, recurring and >3cm TaG1-2) has 80% of recurrence rate and a progression rate of 50% in the following three years of follow-up (6). The prognosis gets worse when recurrence or progression occur.

4.1.2 ETIOLOGY: *RISK FACTORS*

Tobacco smoking is the most important risk factor for bladder cancer, being the responsible etiology in 50% of cases. The risk of bladder cancer increases with the duration and intensity of tobacco consumption. The relative risk for BC mortality due to smoking in second only to lung cancer. The main carcinogens are aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted. These particles promote inflammation, and their metabolism in the bladder culminates in DNA-adduct formation and permanent genetic mutation. Such mutations can activate oncogenes or suppress tumor suppressor genes, promoting carcinogenesis. The mean age of onset of BC suggests a latency period of 30 years from the initiation of smoking to the BC diagnosis. Nevertheless, it has been proved that smoking cessation can reduce the risk of bladder cancer by 40% within 1-4 years, and a complete return to baseline risk by 20 years. (2)(3)

Occupational exposure is the second most important risk factor for BC (10% of cases) and it occurs mainly in industrial plants which process paint, dye, metal, and petroleum products. The principal carcinogens are aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons. (2)

Schistosomiasis is a chronic endemic cystitis based on recurrent infections with a parasitic trematode and it is also a cause of BC (2). It is related to squamous cell bladder cancer, accounting for the 10% of cases of bladder cancer and being more prevalent in Africa (3).

Exposure to ionizing radiation have been shown to increase the risk of bladder cancer; and it is also suggested a weak association between BC and ***cyclophosphamide and pioglitazone*** (2)(3).

The rest of risk factors are schematized in ***figure 4*** but these have not demonstrated an association as strong as the risk factors discussed above.

Figure 4. Principal risk factors of bladder cancer.

4.1.3 HISTOLOGICAL ASPECTS, STAGING AND CLASSIFICATION SYSTEMS

The majority of bladder tumors (>95%) have an epithelial origin (**Figure 5**), being the urothelial neoplasm the most common type followed by squamous and glandular neoplasms (7).

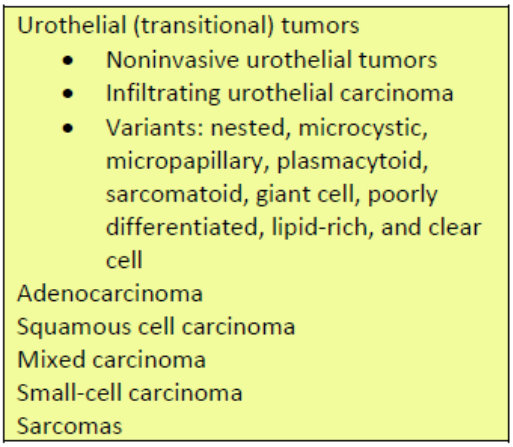


Figure 5. Histological types that may be found in bladder tumors.

Urothelial neoplasms represent about 90% of all bladder tumors and many of them are multifocal at presentation. It exists two different precursor lesions to invasive urothelial carcinoma: *noninvasive papillary tumors* and *flat noninvasive urothelial carcinoma in situ* (CIS) (**Table 1**). **Squamous cell carcinomas** represent the 3% to 7% of BC and is more prevalent in countries where schistosomiasis is endemic. **Adenocarcinoma** of the bladder is exceptional and histologically identical to adenocarcinomas seen in gastrointestinal tract (7).

Table 1. Main characteristics and WHO/ISUP classifications of non-invasive papillary and flat non-invasive urothelial carcinomas.

	Non-invasive papillary tumor	**Flat non-invasive urothelial carcinoma**
Definition	Most common precursor lesion of invasive bladder tumors. It is originated from papillary urothelial hyperplasia.	It is an epithelial lesion with cytologic features of malignancy, so it is considered to be a high grade lesion but is confined to the epithelium.
Mutations	Gain-of-functions mutations: *RAS, FGFR3*	*TP53, RB* mutations
Recurrence & progression	High recurrence but rare progression	Very high recurrence and progression to invasive carcinoma (50-75%)
WHO/ISUP Grades (2016)	• Papilloma • Urothelial proliferation of uncertain malignant potential (papillary hyperplasia) • Papillary urothelial neoplasms of low malignant potential • Papillary urothelial carcinoma, low grade • Papillary urothelial carcinoma, high grade	• Urothelial proliferation of uncertain malignant potential (flat hyperplasia) • Urothelial dysplasia • Urothelial carcinoma in situ
WHO grades (1973)	1. Well differentiated 2. Moderately differentiated 3. Poorly differentiated	

Tumor, Node and Metastasis Classification (TNM)

The last TNM update was in 2017 (8th Edn.), but with no changes about bladder cancer in relation with the 2009 TNM classification approved by the Union International Contre le Cancer (UICC) (**Figure 6**) (**Table *2***). Ta, T1 and Tis are grouped as non-muscle-invasive bladder cancers for therapeutic purposes since all these tumors can be treated by transurethral resection and in combination with intravesical instillations (2).

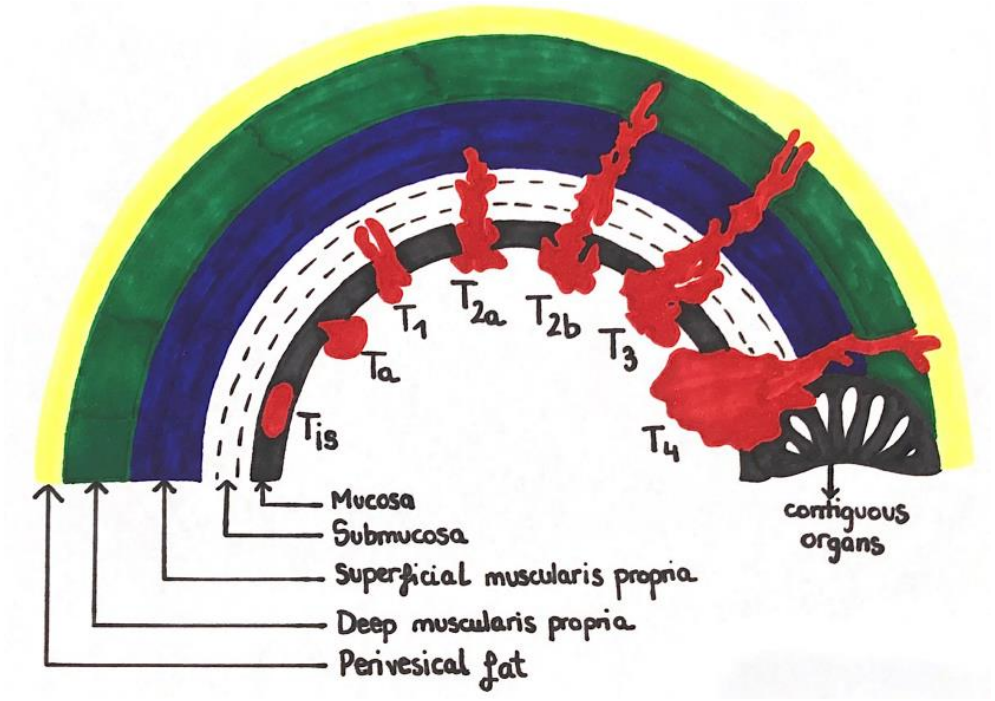


Figure 6. Bladder cancer stages according to the "T" of TNM clasification.

Table 2. Pathologic Stage Classification of urinary bladder carcinoma (2017. 8th Edn.). The "N" and "M" are represented in ***Annex 7***. Adapted from (7).

T (primary tumor)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumor invades pelvic wall or abdominal wall

4.1.4 DIAGNOSIS

PATIENT HISTORY AND PHYSICAL EXAMINATION

Bladder cancer appears in patients **older than 65 years** in approximately 70% of cases. BC affects to **men** principally. It is related to the consumption of **tobacco** (principal risk factor) as well as occupational exposure, use of chemotherapy and pelvic radiotherapy; for that reason, it is mandatory to ask the patient for these risk factors (8).

Signs and symptoms

- **75%** of cases clinically start with **hematuria** (4) (**80-90%**): intermittent, monosymptomatic and with blood clots (6):
    - **Macroscopic hematuria** (70-80%) (6) is strongly corelated with bladder cancer (8) and it is associated to a higher stage when compared with microhematuria (2).
    - **Microscopic hematuria** (20%) (6).
- **Irritative micturition syndrome** (20-30%) (6): symptoms include are urinary urgency and/or frequency and dysuria (inferior urinary tract symptoms) (4). It typically appears in high grade tumor -CIS- or invasive disease (6).
- **Recurring urinary tract infection** (8).
- **Others:** pelvic pain, weight loss, etc. (5)**.**
- ***Physical examination***: It is necessary to examine the abdomen in search of abdominal masses and the presence of inguinal or distant lymphadenopathies. In addition, a rectal examination must be performed in order to rule out bladder extension (6) .

ULTRASOUNDS

US is usually the first diagnosis test used in the *initial management of patients with hematuria*. It permits to detect *superior urinary tract obstruction*, *renal masses* and *bladder lesions larger than 0,5 cm* (6)(8). Nevertheless, US can´t rule out all potential causes of hematuria and reliably exclude the presence of upper tract urothelial carcinoma (2)**.**

CYSTOSCOPY

In cases in which an urothelial carcinoma is suspected, cystoscopy will confirm the affectation of inferior urinary tract (8). It permits to do a diagnosis and to obtain information about the size and number of lesions, their morphology (papillary, sessile, solid and/or with calcifications), base characteristics and also the existence of flat lesions (CIS) (6). It is performed as an outpatient procedure using a flexible (preferred) or rigid instrument with topical intraurethral anesthetic (2).

URINARY CYTOLOGY

It is necessary to perform the cytology on at least 25 mL fresh urine or urine with adequate fixation. First urine in the morning is not a good specimen because cytolysis could be present. Cytology is particularly useful as an adjunct to cystoscopy in patients with high grade/G3 tumors (sensitivity: 84% in G3/CIS vs 16% in G1-2). The interpretation is user-dependent, and it can be impeded by intravesical instillations, stones, urinary tract infections and low cellular yield. In patients with suspicious cytology, it is recommended to repeat the cytology (2).

TRANSURETHRAL RESECTION

The aim of transurethral resection of the bladder (TURB) in TaT1 BC is to make the correct diagnosis and completely remove all visible lesions, so in these cases it is the definitive surgical treatment. In muscle-invasive bladder cancer, transurethral resection of bladder tumor (TURBT) is part of the diagnosis procedure. In some cases, it will be necessary to perform bladder and prostatic urethral biopsies.

- Bladder biopsies

Biopsies should be taken from abnormal urothelium suspicious of carcinoma *in situ* (velvet-like, reddish areas) and also from normal-looking mucosa in patients with positive urine cytology, or with a history of high grade/G3 NMIBC and in tumors with non-papillary appearance. To obtain representative mapping of the bladder mucosa in cases of normal looking urothelium, biopsies should be taken from: trigone, bladder dome, right, left, anterior and posterior bladder wall. Photodynamic diagnosis is a useful tool to target the biopsy if the equipment is available (2).

- Prostatic urethral biopsies

Biopsies of prostatic urethra should be taken in cases of bladder neck tumor, if there is a positive cytology without evidence of tumor in the bladder, if bladder carcinoma in situ is present or suspected, or if abnormalities of the prostatic urethra are visible (2).

- Second transurethral resection

It will be necessary to perform a second resection at 2-6 weeks from the initial TURBT in those patients with no presence of detrusor muscle in the specimens (except Ta-low grade/G1 tumor or primary CIS), T1 tumors (especially if they are HG tumors) and incomplete initial TURB (2).

URINARY MOLECULAR MARKER TESTS

Because of low sensitivity of cytology a lot of urinary tests have been developed; however, none of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines (2). Nowadays, urinary molecular marker tests may be used as an adjunct to cystoscopy in order to stratify bladder tumors according to their progression and recurrence risks (6).

IMAGING:

- Computed tomography urography:

It will confirm the affectation of superior urinary tract, when an urothelial carcinoma is suspected (8). Even though the incidence of a concurrent urothelial tumor in superior urinary tract is low (1,8%), it can reach to 7,5% when the tumor is on the trigone (6). In general, in patients with bladder cancer we do CT urography after transurethral resection (TUR) is performed and the pathologic analysis determine that it is an infiltrative bladder tumor (≥ T2).

- Multi-parametric magnetic resonance imaging:

It has not yet established in BC diagnosis and staging (2).

ACCORDING TO FINDINGS:

- Abdominopelvic CT is useful in order to stage muscle-invasive tumors (locoregional and distant metastases) (6).

- Bone gammagraphy or CT-PET scan if there is suspicion of bone metastases or an increasing of alkaline phosphatase (4).

OTHERS:

- Fluorescence cystoscopy or photodynamic diagnosis (PDD): it is performed using violet light after intravesical instillation of hexaminolaevulinic acid or 5-aminolaevulinic acid. It is more sensitive for the detection of malignant tumor such as CIS (2).
- Narrow-band imaging: it enhance the constrast between normal urothelium and hypervascular cancer tissue (2).

4.1.5 SCREENING

It has not yet been stablished in general population, even in important tobacco consumers or in patients expose to bladder carcinogens, because there is not enough evidence (8).

4.1.6 RISK GROUP CLASIFICATION (EORTC) & TREATMENT OF NON-MUSCLE-INVASIVE BLADDER CANCER

In patients suspected of having bladder cancer, to perform a transurethral resection of the bladder followed by pathologic investigation of the obtained specimens is the initial treatment step. In patients with bladder tumors suspected or diagnosed of NMIBC, after TURBT, it is necessary the application of intravesical therapy based on chemotherapy or immunotherapy. The type of intravesical adjuvant treatment depends on the Risk Groups Classification by the EORTC (**Table *3***) (**Figure 7**). Mitomycin C is used as the main chemotherapy agent and must be instilled in each patient immediately after performing TUR, except in those cases of vesical perforation, pregnant women, allergy, tumors that seem to be infiltrative during the intervention, patients with positive results in urine cytology and recurrent tumors from previous high-grade tumors, because it has proved to reduce the recurrence rates in a 13%. Once we have the results of the pathological analysis, it will be necessary to administer the most suitable adjuvant therapy. It is necessary to counsel smokers with suspicious or confirmed non-muscle-invasive bladder cancer to stop smoking.

Table 3. Risk group clasification (EORTC risk tables) and treatment. PUNLMP= papillary urothelial neoplasm of low malignant potential; BCG= Bacillus de Calmette-Guérin. Adapted from (9).

Risk group	Characteristics	Treatment recommendation
Low risk tumors	Primary, solitary, TaG1 (PUNLMP, LG), <3cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB
Intermediate risk tumors	Those tumors no classified in the other categories	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and an expected EORTC recurrence score of <5, one immediate instillation of intravesical chemotherapy after TURB. In all patients 1 year full-dose BCG treatment (induction* plus 3-weekly instillations at 3, 6 and 12 months) or instillations of chemotherapy for a maximum of 1 year. *BCG induction = weekly instillations for 6 weeks
High risk tumors	T1, G3/high grade, CIS tumors or Ta, G1-2, multiples, recurrent and >3cm (all conditions present)	Intravesical full-dose BCG instillations for 1-3 years
	Very high-risk subgroup:	
	T1 and high-grade tumor associated to CIS	Radical cystectomy should be considered. In those who refuse or are unfit for radical cystectomy, intravesical full-dose BCG instillations for 1-3 years.
	T1, high grade, multiple and/or large tumor	
	T1, high grade and recurrent tumor	
	High grade tumor with CIS in prostatic urethra	
	Histological variants (micropapillary, plasmocytoid and sarcomatoid)	
	Lymphovascular invasion	

4.1.7 NON-MUSCLE-INVASIVE BLADDER CANCER FOLLOW-UP

- In patients with **low-risk** Ta tumors cystoscopy should be done at three months. Urine cytology is recommended. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years (2).
- In patients with **high-risk** tumors cystoscopy and urinary cytology must be done at three months. If negative, these tests should be repeated every 3 months for 2 years and, then every six months until 5 years. After 5 years, yearly (2).
- Patients with **intermediate-risk** tumors should undergo cystoscopy and cytology with an individualized schedule (more or less 3 months after TURB) (2).
- Yearly CT urography to study upper urinary tract is recommended for high-risk and very high-risk tumors (2).
- During follow-up in patients with no visible tumor in the bladder and positive cytology, mapping biopsies or PDD-guided biopsies and searching for extravesical locations (CT urography, prostatic urethra biopsy) are recommended (2).

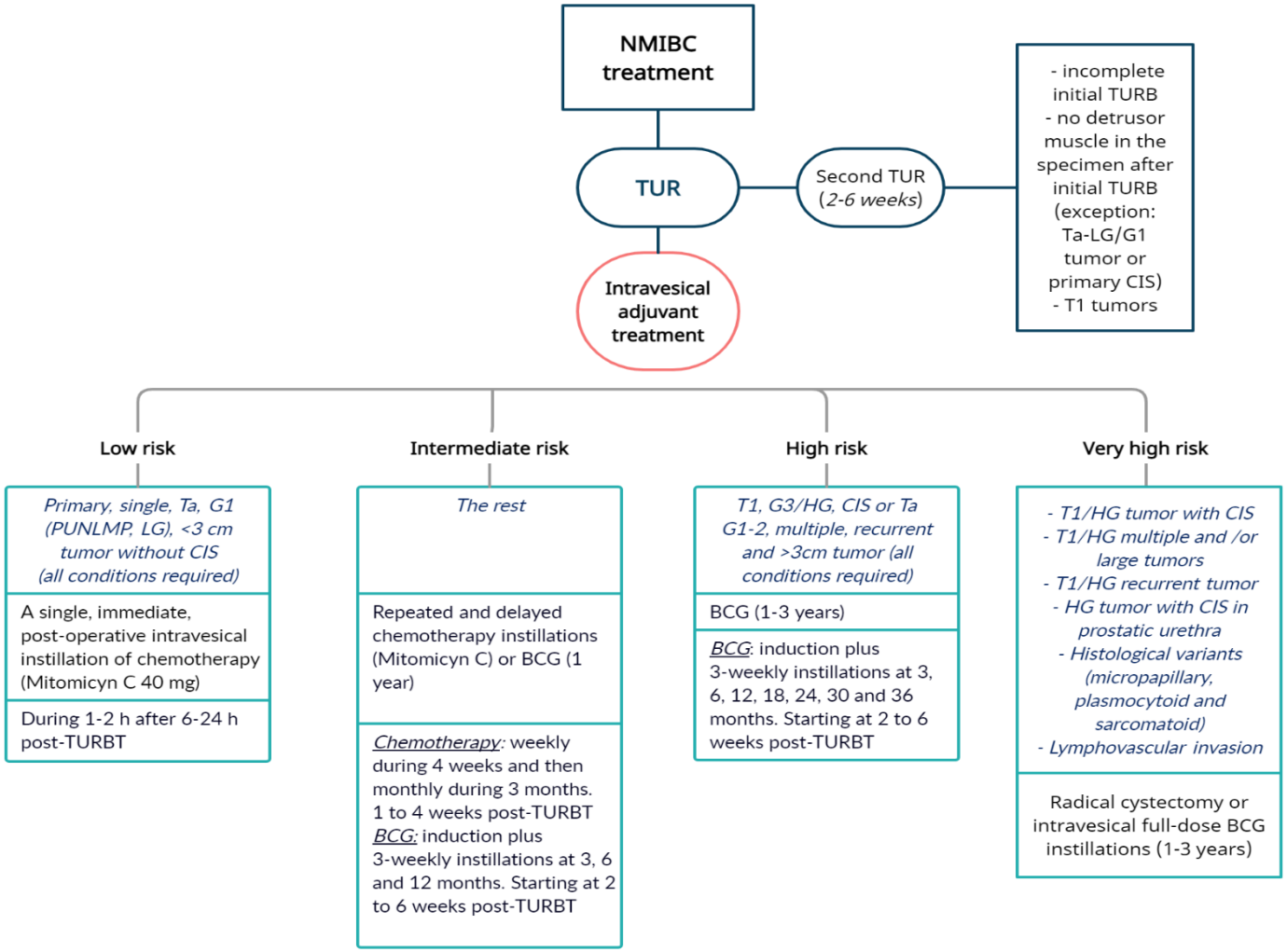


Figure 7. Therapeutic management of patients with bladder cancer.

4.1.8 RECURRENCE AND PROGRESSION RATES OF NON-MUSCLE-INVASIVE BLADDER CANCER

The data shown below are approximate percentages for each risk group. EAU guidelines about non-muscle-invasive bladder cancer (TaT1 and CIS) recommend applying the EORTC risk tables and calculator in individual patients for the prediction of the risk tumor recurrence and progression after transurethral resection of the bladder. The application of intravesical chemotherapy immediately after TURBT reduce about 13% the risk of recurrence. In addition, with the application of repeated chemotherapy instillations this number increases. Bacillus Calmette-Guérin (BCG) therapy may reduce the risk of tumor progression and BCG maintenance treatment appears to be significantly better in preventing recurrences than chemotherapy but it causes more side effects (2).

Table 4. Recurrence and progression rates of non-muscle-invasive bladder cancer. Adapted from (9).

Risk Group	**Probability of recurrence at 1 year (% and 95% CI)**	**Probability of recurrence at 5 years (% and 95% CI)**
Low	15 (10-19)	31 (24-37)
Intermediate	24 (21-26)	46 (42-49)
High	38 (35-41)	62 (58-65)
Very high	61 (55-67)	78 (73-84)
	Probability of progression at 1 year (% and 95% CI)	**Probability of progression at 5 years (% and 95% CI)**
Low	0.2 (0-0.7)	0.8 (0-1.7)
Intermediate	1 (0.4-1.6)	6 (5-8)
High	5 (4-7)	17 (14-20)
Very high	17 (10-24)	45 (35-55)

4.2 TRANSURETHRAL RESECTION

Transurethral resection of bladder tumor (TURBT) is one of the most common urological operations. In 1910, Beer first reported endoscopic treatment of bladder cancer. Jones and Swinney described endoscopic removal of bladder cancer using a resectoscope for first time in 1962. Before to this, most large tumors were removed by cystostomy. In addition, in 1978, the introduction of video endoscopy provided a closer supervision. Nowadays, transurethral resection (TUR) is used for the management of bladder tumors and prostate pathology such as benign prostatic hyperplasia (10).

The main objectives of performing a transurethral resection of a bladder tumor are:

- To obtain tissue samples in order to do a proper pathologic diagnosis, which consists in grading and staging the bladder tumors.
- To reduce the clinical symptomatology such as hematuria.
- To resect all visible growth inside the bladder. In case of non-muscle-invasive bladder tumors, TUR is in general the definitive surgical treatment.

Even though TURBT has some risks, it is considered a **minimally invasive technique**. There are two main modalities of electrocautery in TUR: monopolar and bipolar transurethral resection. Monopolar transurethral resection of the bladder (mTURB) has been the gold standard for many years with good results. Nevertheless, bipolar transurethral resection has been gaining importance in recent years. The main characteristics of each system are described below.

4.2.1 PRINCIPAL DIFFERENCES BETWEEN MONOPOLAR AND BIPOLAR TRANSURETHRAL RESECTION

<u>Technical differences</u>

The path of the electric current in monopolar electrosurgery is from the active loop, through the patient, until the indifferent electrode (the grounding pad) positioned on the patient´s skin and then, back to the electro-surgical unit to complete the circuit. In contrast, in bipolar electrocautery the large return electrode of the monopolar modality is replaced by a second small electrode placed within the same loop. The path of the

current is from the active loop, through the patient´s bladder tissue, to the second electrode placed very close in the same loop, and then back to the electrosurgical generator. As the two electrodes are together in the instrument, the patient is excluded from the electrical circuit (**Figure *8***) (11, 12, 13).

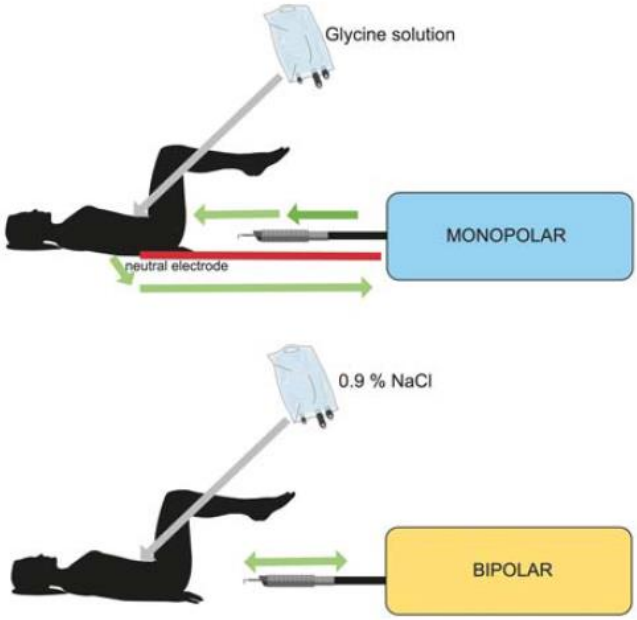


Figure 8. Monopolar vs Bipolar transurethral resection of bladder tumor. Extracted from (14).

Plasmakinetic monopolar resection is performed with hypotonic glycine, sorbitol or mannitol for irrigation instead of the isotonic saline used in bipolar electrocautery (12). The role of irrigation solution is to distent the bladder, wash away blood and resected tissue and thus clear the surgical site (15). The use of isotonic saline helps to avoid transurethral resection syndrome (TUR syndrome) when we use bipolar electrocautery (12). TUR syndrome is a systemic complication of monopolar TUR, caused by excessive absorption of electrolyte-free irrigation fluids and resulting in acute hypervolemia and hyponatremia. This syndrome may potentially cause neurologic symptoms, pulmonary edema, cardiovascular compromise, and death. The diagnosis should be rapid (spinal anesthesia as technique of choice, allowing early detection of neurological disturbance), the surgery should be finished as quick as possible and the treatment of severe cases is based on correcting electrolytes and making patient hemodynamically stable (15).

Because of that, related to the intervention time, monopolar cannot be used more than 45 minutes or 1 hour of intervention, in contrast to bipolar equipments, which have no time limitation. It is a factor to be considered in large, difficult to access or very numerous tumors.

Moreover, in monopolar TURBT, electrical energy is directed into the tissues, where creates a temperature higher than 300ºC due to the electrical resistance (12). Heat generated allows the cutting of tissues but also leads to desiccation of surrounding cells, which often results in the presence of thermal artifact (TA) in resected bladder tissues. TA can hinder and obscure important characteristics of both the tumor and the underlying and surrounding bladder structures and then, to limit the pathologist´s ability of doing an appropriate diagnosis and staging (**Table 9**) for the best treatment recommendation in each case (16). However, in bipolar systems the radiofrequency current transform the conductive medium into a plasma field of highly ionized particles dissociating the organic molecular bonds between the tissues and reducing it into elementary molecules. In this case, the temperature rises only up to 40 to 70ºC, which can reduce the thermal damage to the surrounding tissues (11, 12).

Differences in terms of safety and efficacy

According to several recent studies, bTURB seems to be more efficient and safer than mTURB in the treatment of NMIBC, and may be used as a preferable substitute for conventional monopolar electrocautery (12).

The bTURB allows to have a more precise cutting and more reliable hemostasis ability, with shorter operation time, shorter hospital stay, less bleeding, less thermal damage, short catheterization period and fewer complications such as obturator nerve reflex, bladder perforation and apparition of TUR syndrome (12).

The 2-years recurrence rate of bladder cancer was higher in mTURB group in a meta-analysis (12). This could be explained by the reducing of residual lesions using bTURB due to its more accurate cutting ability and its lower occurrence of perioperative complications. However, these results remained questionable because the sensitive analysis of recurrence rate indicated that this result was not stable, and there was lack

of other evidence that supported this conclusion. Something similar occurred with other parameters. For instance, the difference in operation time was of a few minutes and catheterization time of one day. These results comparing mTURB and bTURB were statistically significant but revealed limited clinical significance (12). In another study, there were no significant differences in recurrence rate comparing the two procedures. Despite this, they said that a large-scale, multicenter, randomized controlled studies were needed before final clinical recommendations (17).

Table 5. Comparison between monopolar and bipolar current for TURB. Adapted from (14).

Variable	Monopolar	Bipolar
Dispersive electrode pad	Yes	No
Energy	High	Low
Voltage	High	Low
Working medium	Glycine	Saline
Temperature at thermal effect (ºC)	300-400	40-70
Time of resection	Limited	Extended (not strictly limited)
TUR syndrome	Common	Rare
Obturator jerk	Common	Rare
Quality of hemostasis and coagulum	Poor	Good

4.2.2 THERMAL ARTIFACT

Thermal artifact (TA) is defined as the distortion of the tissues microscopic structure due to the heat generated by the electrocautery loop of monopolar or bipolar systems. It has been proved that both types of electrocauteries may create TA in the sample and in the surrounding tissues, and this TA increases when the tumor is smaller, making almost impossible to obtain enough sample to analyze in tumors < 0.5 cm. Nevertheless, some debate has appeared during the years about if it exists a difference in the degree of this TA when monopolar or bipolar electrocautery is used and, what is more important, if this variation can affect the pathological analysis.

Some studies have shown that there is no difference between using monopolar or bipolar electrocautery for the diagnosis and treatment of bladder tumors in terms of thermal artifact (17, 18, 16, 19, 20). In all of them, the pathologist was blinded to the type of intervention and authors could concluded that bipolar resection was well suited for TURBT and that the histologic tissues sampled were of similar quality to those obtained with standard monopolar TURBT for a reliable diagnosis.

Nevertheless, some articles have shown that, with the use of bipolar TUR instead of monopolar electrocautery, thermal artifact may be reduced, and this can facilitate the histologic analysis (12, 11, 15, 21, 22, 23). In a comparative study that evaluated the TA in the resected specimens of monopolar and bipolar transurethral resection of bladder tumors (11), it was seen that bipolar resection produced lesser degree of TA, better preservation of cytoarchitecture and thereby helped in correct interpretation of grade and depth of invasion. Also, it was easy to identify muscle invasion without the need for repeat histological sections of BTs resected by bipolar energy. Even though bipolar energy proved to be better, there was no difficulty noticed during histopathological examination of resected specimen in any group and none grade 3 (**Figure 10**) thermal damage according to the WHO classification (**Table 8**). The depth of penetration was more in monopolar resection, but the thermal spread was higher too (**Figure 9**) (11).

It has also been seen that cautery artifact can obscure the ability to determine both lamina propria and muscularis propria invasion, but more frequently affected the determination of the last one (25). This is important because the pathologist may classify a bladder tumor as a non-muscle-invasive cancer when actually is a T2 o > T2 stage, which implies a different prognosis and treatment.

Related to the presence of deep muscle and its pathological analysis, which represent a cornerstone in the further management of bladder tumors, some randomized studies have shown that the deep muscle was present in 100% of bipolar specimens but 90-100% of monopolar ones (11). However, in one of the studies the thickness of deep muscle when bipolar system was used was thinner compared to monopolar (19). In the study of Jeremy Yuen-Chun et al. (23) a superior detrusor muscle sampling rate was

obtained when they used bipolar TURBT , but it was significantly associated with larger tumor size (the operating surgeon had to resect wider and deeper for larger tumors compared with smaller ones) and female sex (technically easier).

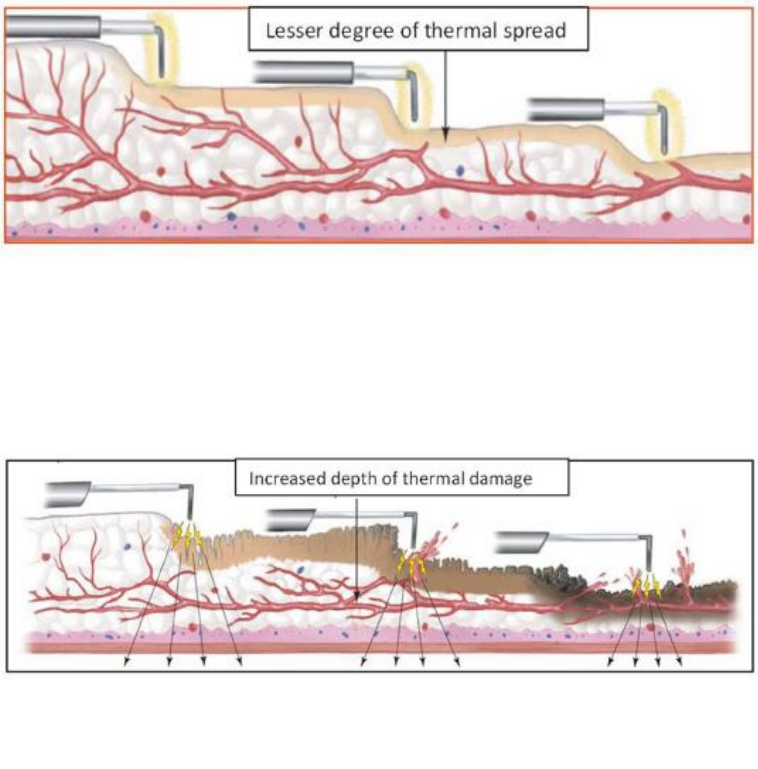


Figure 9. Thermal spread and its depth in Bipolar (A) and monopolar (B) electrosurgery. Extracted from (11)

Measurement of thermal artifact

It exists some evaluation measures than can be used in order to assess the thermal damage in tissue samples. The most common used in the studies is the WHO classification (**Table 8**) (**Figure 10**), which divides the TA into 4 grades; however, there are others that have been used in the literature (**Table 6**).

Table 6. Examples of evaluation measures of thermal artifact in samples.

Reference	Evaluation measures
Bolat et al. (26)	Thermal damage was classified into 2 groups depending on the quantity of cautery artifacts: mild TA was defined as involving <50% of entire specimen, and severe >50%
Murugavaithianathan et al. (27)	TA were analyzed for quantity (into 3 grades) and quality (WHO classification)
Venkatramani et al. (22)	Severe artifact was defined as more than 50% cautery artifact in most chips
Yang et al. (19)	TA was categorized into 3 groups: grade 1 (TA involving <1/3 of entire specimen), grade 2 (1/3 to 2/3) and grade 3 (>2/3) (**Figure *11***)
Kumar et al. (20)	The severity of TA was graded as absent (none of resected specimen was involved), mild (<25%), moderate (25-50%) and severe (>50%)

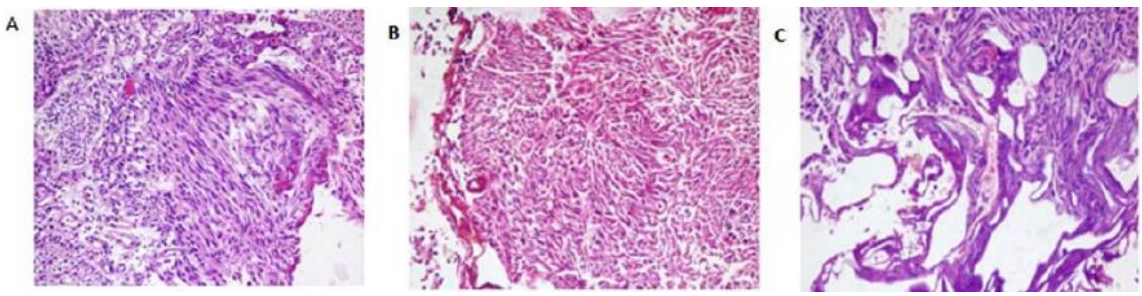


Figure 10. WHO classification of thermal artifact. A= grade 1; B= grade 2; C= grade 3. Extracted from (27).

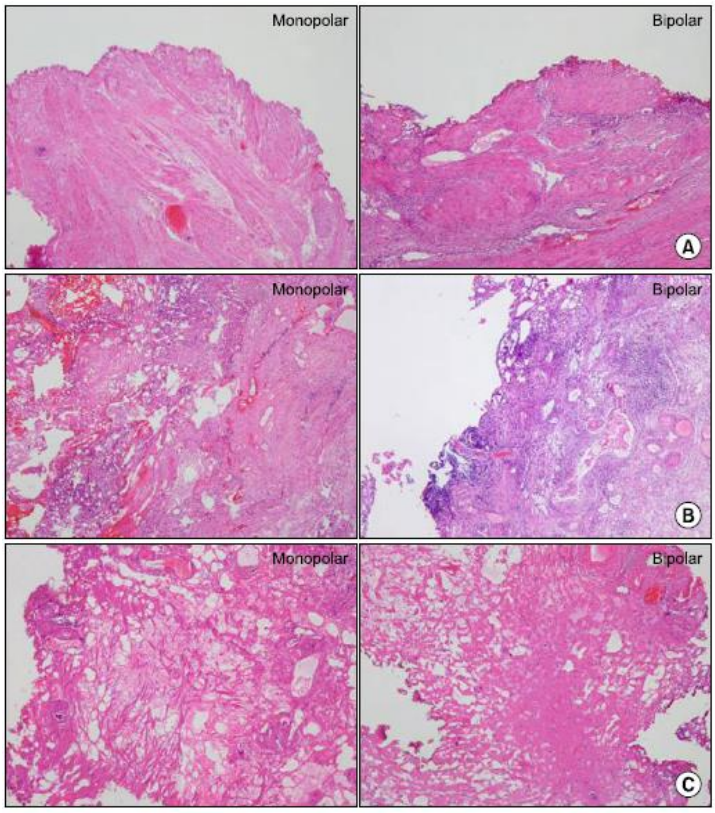


Figure 11. Thermal artifact seen with bipolar and monopolar current. (A) Grade I: involving <1/3. (B) Grade II: involving 1/3- 2/3. (C) Grade III: involving >2/3. Extracted from (19).

5. JUSTIFICATION

Bladder cancer is the 10th most common diagnosed malignant neoplasm worldwide (2), its incidence is continuously rising, especially in developed countries (3) and it is strongly associated with tobacco smoking. Near to a 90% of bladder neoplasm are urothelial carcinomas (3) and, approximately 75% of patients initially present with "superficial" non-muscle-invasive bladder cancer (5). In general, this stage have a good prognosis, but their main problem is that many of them recur and some may progress to a more advanced stage. Despite adjuvant intravesical treatment after transurethral resection, which have been shown to decrease the risk of recurrence, more than 50% of non-muscle-invasive affected patients experience recurrence and 10-15% progress to muscle-invasive BC (5), but these percentages varies across the tumor risk category. The prognosis gets worse when recurrence or progression occur**.**

Transurethral resection is the cornerstone of the initial management of bladder cancer since it allows to do a pathologic diagnosis, which consists of grading and staging, to reduce the clinical symptomatology such as hematuria, and it is also the definitive surgical treatment in most of non-muscle invasive bladder cancer cases. Even though TURBT has some risks, it is considered a minimally invasive technique. The pathological analysis of the samples obtained by TURBT is essential in determining whether more radical treatment is necessary or a conservative treatment is sufficient. Because of that, the endoscopic removal of bladder tissue must ensure that the tumor is safely and completely removed; therefore, TURBT must be performed in a meticulous way, without excessive destruction of the tumor tissue (thermal artifact) (18). In addition, a sufficient detrusor muscle sample has to be obtained from TURBT, not only for proper staging but also because the presence of detrusor muscle could serve as a predictor of early recurrence, recurrence-free survival and progression-free survival (23).

Nowadays, it exists two main electric TURBT modalities: *monopolar* and *bipolar* TURBT. Monopolar TURBT has been the gold standard for many years but, recently, bipolar TURBT has become more relevant and used. Bipolar TURB seems to be safer, more

efficient and presents several clinical and pathological advantages when is compared with conventional mTURB (12).

Most of the studies support that there is less thermal artifact in the tissue sample when bipolar TURBT is used due to the fact that bipolar systems use modest temperatures between 40 to 70º (300ºC with monopolar). However, in some of them this issue is not completely established or the difference between using bTURBT against mTURBT is not clinically significant (19) .

Related to the recurrence and progression rates, in a meta-analysis the 2-years recurrence rate of bladder cancer was higher in the monopolar TUR group (12). However, these results remained questionable because the sensitive analysis of recurrence rate indicated that this result was not stable, and there was lack of other evidence that supported this conclusion.

In summary, what is actually important is that none of these articles studied the relation between the severity of the thermal artifacts and their impact in the understaging and undertreating of bladder cancer and how this affects to the recurrence and progression rates.

For that reason, the aim of this protocol is to study if the use of bipolar versus monopolar transurethral resection, in those patients diagnosed of endovesical lesion with papillary morphology highly suspicious of urothelial carcinoma, can lead to a decrease in the recurrence and progression rates due to a better pathologic diagnosis and treatment because of the lesser quantity of thermal artifact obtained in the tissue samples. We will study these percentages according to 3 risk groups (high, intermediate and low risk of recurrence) since the characteristics of the tumor itself have an impact on the probability of recurrence and/or progression. If our study shows that when bipolar TUR is used there is a decrease in the recurrence and progression rates, this will imply that every hospital that perform TUR should invest in bipolar electrocautery systems, as this would mean a better prognosis for the patient, or otherwise refer them to hospitals where they can be treated with bipolar transurethral resection.

6. HYPOTHESIS

Hypothesis 1: The use of bipolar energy in transurethral resection of the bladder permits to resect the tumoral tissue more accurately in patients with non-muscle-invasive bladder cancer, obtaining lesser quantity of thermal artifact in tumor samples compared to the use of monopolar energy.

Hypothesis 2: The obtaining of samples in a better condition (with less cautery artifact) using bipolar transurethral resection, compared with the use of monopolar current, allows a more precise pathologic diagnosis (staging and grading) and, consequently, permits to offer a suitable treatment for patients with non-muscle-invasive bladder cancer.

Hypothesis 3: The possibility of offering a more accurate pathologic diagnosis (staging and grading) and a more suitable treatment when bipolar transurethral resection is used, compared with monopolar systems, entails a decrement in the recurrence and progression rates in each risk group (high, intermediate and low risk) in patients diagnosed with non-muscle-invasive bladder cancer.

7. OBJECTIVES

Objective 1 (related to hypothesis 1): To evaluate whether the degree and severity of thermal artifact is lower in tumoral samples with the use of bipolar transurethral resection, when compared to monopolar energy, related to the management of patients with non-muscle-invasive bladder cancer.

Objective 2 (related to hypothesis 2): To determine if bipolar transurethral resection allows a more accurate pathologic diagnosis (staging and grading), due to less thermal artifact, when is compared to monopolar systems, in patients diagnosed with non-muscle-invasive bladder cancer.

Objective 3 (related to hypothesis 3): To demonstrate that the use of bipolar transurethral resection, compared with monopolar current, entails a decrement in the recurrence and progression rates in each risk group (high, intermediate and low risk) in patients diagnosed with non-muscle-invasive bladder cancer, due to a more accurate pathologic diagnosis.

8. METHODOLOGY

8.1 STUDY DESIGN & STUDY SETTING

This study will be a multicenter, longitudinal, prospective, parallel-group, double-masked, randomized and controlled clinical trial.

The study will be carried out in 4 hospitals from Cataluña: Hospital Josep Trueta (Girona), Hospital Santa Caterina (Girona), Hospital Vall d´Hebron (Barcelona) and Hospital Clínic (Barcelona). These hospitals are reference centers in Cataluña and where most of cases of bladder cancer are treated and followed-up.

In each center we will assign a principal researcher (a urologist) who will propose to the patients to enter into the study and will follow them until recurrence or progression, if it occurs; a urological surgeon for performing the TURBT and two senior pathologists specialized in genitourinary system, who will analyze the bladder tissue samples. A study coordinator and a statistician will be hired. The first one will coordinate the four centers so that they adhere homogeneously to the protocol and in order to obtain a good communication and coordination between all of them. The statistician will be in charge of randomizing patients and interpreting the results of the study.

The recruitment of patients will last about 15 months, with subsequent follow-up of them for 12 months with cystoscopy and urine cytology. In this study the 3 risk categories (high, intermediate and low-risk NMIBC) will have the follow-up schedule recommended in the European Guidelines in order to determine the percentage of recurrence and progression. In total, the entire study will last about 3 years and 9 months.

8.2 STUDY SUBJECTS

To know which patients will participate in this study, we have to define our population of interest. The study subjects will be patients with a bladder tumor (or multiples) suggestive of urothelial carcinoma, newly diagnosed, and that meet all the inclusion criteria and none of the exclusion criteria.

The patients will be selected and included in the study on the first day come to the urologist consult after the realization of bladder ultrasounds, cystoscopy, and a urine cytology and the diagnosis of bladder tumor suspicious of urothelial carcinoma, during a recruitment period of one year and three months.

8.2.1 INCLUSION CRITERIA

Patients may be included in the study only if they meet all of the following inclusion criteria:

- Ability to understand and the willingness to sign a written informed consent document.
- Patients ≥ 18 years.
- Patients with primary presentation (newly diagnosed) of one or several bladder tumors > 0,5 cm and with papillary morphology, highly suggestive of urothelial carcinoma:
    - The diagnosis will be made from bladder ultrasound and a cystoscopy. Urine cytology may be either positive or negative.
- Patients with pure urothelial carcinoma in histological analysis (100% urothelial carcinoma).
- Laboratory test (≤ 2 weeks before the participation to the study):
    - Adequate hematologic function: hemoglobin ≥10 g/dl, Leukocytes > 3,000/mcL, neutrophils ≥ 1,500 cells/ul and platelets ≥ 100,000 cells/ul.
    - Normal results in coagulation tests.

8.2.2 EXCLUSION CRITERIA

Patients will be excluded from the study for any of the following reasons:

- Patients with recurrent bladder tumors or with personal history of bladder cancer.
- Any patient with a single bladder lesion < 0,5cm.
- Patients with bladder lesions highly suspicious of carcinoma *in situ* (CIS): presence of flat tumors or no abnormalities at cystoscopy in a patient with positive cytology and/or with irritative micturition syndrome (*urinary urgency*

and/or frequency and dysuria) as predominant clinical profile. This criterion will be considered at the first step of the study (recruitment of patients).

- Patients diagnosed of muscle-invasive bladder cancer (T2) by the pathologist after transurethral resection of the bladder.
- Patients who, according to the pathological analysis, present a papilloma or hyperplasia (related to ISUP classification) after transurethral resection of the bladder tumor.
- Patients who present a concomitant carcinoma *in situ* according to the pathological analysis of the tissue obtained by multiple randomized bladder biopsies*.

  *Multiple bladder biopsies will be performed in patients with positive urinary cytology in combination with transurethral resection of the bladder.
- Histological variants apart from urothelial carcinoma such as nested variant, microcystic variant, squamous carcinoma or adenocarcinoma (**Figure 5**). Even in patients with a bladder tumor that have a percentage of urothelial carcinoma and a percentage of another variant will be excluded.
- Seriously ill patients (Karnofsky score < 50) (***Annex 6***).
- Any patient with uncontrolled hemorrhagic diathesis or coagulopathy (INR>2).
- Any obstruction in the inferior urinary tract that does not allow to perform the transurethral resection of the bladder.

8.2.3 WITHDRAWAL AND REPLACEMENT OF PATIENTS

Every effort should be made within the bounds of safety and patient choice so that each patient completes the study. Patients who start the follow-up should continue to be followed for 1 year in order to assess the percentage of recurrence and progression as per protocol, unless there is a justified reason. Motives for patient removal from the study include:

- Request of the patient or the patient´s legal representative.

- Patients who want to do the intervention (TURBT) and/or the follow-up in another hospital.
- Patient lost to follow-up. A patient should be considered lost to follow up only after multiple efforts to contact the patient and after the failure of the patient to attend scheduled visits.

A record of the patients that leave the study should be noted with their documents as well as the reason.

Replacement of patients is possible during the period of recruitment in order to have enough people, as study includes patients by to consecutive sampling.

8.3 SAMPLING

8.3.1 SAMPLE SELECTION

A non-probablistic consecutive method will be carried out, involving all patients meeting the inclusion criteria and none of the exclusion criteria and who are treated in the hospitals participating in this study.

8.3.2 SAMPLE SIZE

We estimated the sample size using the free online software GRANMO, and the setting for two independent proportions.

In our study, we will have 2 groups of intervention (monopolar and bipolar transurethral resection). We will also classify patients diagnosed with non-muscle-invasive bladder by transurethral resection in 3 risk groups (high, intermediate, and low risk), with different recurrence and progression rates inherent to their characteristics. We have assumed an alpha risk of 0.025 and a beta risk of 0.2 in a two-sided test. Estimated loss at follow up was 0.1 (10%). For these numbers, GRANMO recommended the following subjects for each group of intervention and each risk category to be sure that there is a significant difference (≥ 15%) between groups:

- High risk: 197 subjects are necessary in the first group (monopolar TUR) and 197 subjects in the second (bipolar TUR).
- Intermediate risk: 123 subjects are necessary in the first group and 123 subjects in the second.
- Low risk: 34 subjects are necessary in the first group and 34 subjects in the second.

This is a total of 708 subjects. However, during the study about a 20% of the initial subjects will be excluded because they will have a T2 bladder cancer (infiltrative stage), a concomitant carcinoma *in situ*, another histological variant different from pure and classic urothelial carcinoma or will have an hyperplasia or papilloma, according to literature. For that reason, we need to increase our initial sample size to **850 subjects** (a 20% more).

8.3.3 ESTIMATED TIME OF RECRUITMENT

Based on the reference population of this study and the incidence of the disease to be treated, we estimated that it will take about **15 months** to recruit the necessary 850 subjects.

8.3.4 RANDOMIZATION METHOD

Once the patients are recruited and we have their urine cytology results, we will classify them in two groups according to if the urine cytology is positive or negative. This is because those with positive urine cytology will undergo transurethral resection of the bladder in combination with multiple randomized bladder biopsies, as recommended in the guidelines. Then, he or she will be assigned to one of the 2 groups of intervention randomly (monopolar or bipolar transurethral resection). All patient´s data will be confidentially maintained by assigning every patient an identification number which will be generated automatically by the software.

8.3.5 MASKING TECHNIQUES

Usually, patients involved in clinical trials don´t know which procedure is made to them and neither the professional who treats the patient knows what treatment the patient is undergoing. Unfortunately, as this is a surgical clinical trial, the blinding of the surgeon is not possible. However, theoretically this does not affect the results of our study. The same occurs with the patients; we will not blind them because this does not affect to the results of the study.

In order to reduce the possible bias, the pathologists that analyze the tumoral samples and the biostatistician in charge of evaluating the procedure results will be blinded, not knowing which modality of TUR has every patient undergone.

8.4 STUDY VARIABLES

Dependent variables:

- **Recurrence and progression rates**:

These are the *principal dependent variables* because they are the main objectives of this study.

- **Recurrence** is defined in our study as the reappearance of bladder lesions (one or multiples) highly suspicious of urothelial carcinoma during the *follow-up* of patients *previously diagnosed with NMIBC*; this is after ***12 months from TUR*** (1 year) in our study. These lesions may be on the previous tumor bed or in any location of the bladder, may be unique or multiples and must have a papillary morphology. The diagnosis will be made by *cystoscopy* and *urine cytology*. In addition, it is mandatory that the confirmation cystoscopy realized 2 weeks after initial TUR determine no presence of any residual bladder lesion.
- **Progression** is defined as:
    - An increase in **histological grade** of lesions previously categorized as low-grade (G1 → G2 → G3 // PUNMLP → LG → HG) determined by the pathologic analysis of samples obtained from TUR in the recurrent cases.
    - An increase in **infiltration depth** of bladder lesions determined by the pathologic analysis of samples obtained from TUR in the recurrent cases:
        - Patients previously diagnosed with NMIBC and categorized as *Ta* stage (confined to mucosa) with *current* bladder tumors categorized as *T1* (confined to submucosa) or *T2** (infiltrative stage).
        - Patients previously diagnosed with NMIBC categorized as *T1* stage (confined to submucosa) with current bladder tumors categorized as *T2** (infiltrative stage).

    * TURBT allows to identify at most T2 bladder tumors because during the procedure we can only obtain samples until the muscularis propria (detrusor muscle). If the tumor infiltrates the superficial muscularis

propria, it will be classified as a T2a tumor. However, if the tumor infiltrates not only the superficial but the deep muscularis propria, it will be classified as a T2b tumor. In order to investigate whether a bladder tumor categorized as T2 by TURBT is actually a T3 or T4 tumor, it is necessary to perform a CT-urography, but this is out of our study.

These variables will be evaluated by the principal researcher (urologist) during the follow-up consultation who will not be blinded to the type of electrocautery used. The evaluation of these variables will be made by risk groups (high, intermediate and low risk), because each of them have a different inherent risk to recur and progress related to their characteristics. The measurement is schematized in the **Figure 20** and explained in the section "*Data Collection and study circuit*". In summary, each risk group will receive a follow-up schedule recommended by the European guidelines with cytology and cystoscopy and, at one year of follow-up, we will quantify the percentage of patients who present recurrence. These patients will undergo transurethral resection and anatomopathological analysis. Those who present progression will constitute the percentage of progression.

- **Presence of thermal artifact in tumor tissue samples**:

This is an **intermediate dependent variable** because we will evaluate the thermal artifact (TA) in tumor tissue samples with the objective of determining if it exists qualitative differences in this TA with the use of bipolar versus monopolar electrocautery and if these differences have an impact over the recurrence and progression rates at 1 year post-TURB in patients diagnosed with NMIBC.

- **Thermal artifact** is defined in our study as the distortion of microscopic structure in bladder tumor tissue samples because of the heat generated by the electrocautery loop of bipolar and monopolar TUR systems. This TA may be classified in different grades and may hinder the pathological analysis of bladder tumor tissue samples. Each tissue sample will be evaluated by two senior pathologists specialized in genitourinary system in each hospital. Moreover, the pathologists will be blinded to the technique of surgery (bipolar or monopolar

TUR). Each pathologist will have a checklist (***Annex 1***) with several items to evaluate in every resected specimen; one of the items will be the "*Thermal artifact*". TA will be analyzed in a qualitative manner (**Table *7***).

Table 7. Measurement of thermal artifact (TA).

QUALITATIVE		
Tissue layer	Which tissue layer is more affected by TA?	▪ Epithelium ▪ Submucosa or lamina propria (connective tissue) ▪ Muscularis propria (detrusor muscle)
World Health Organization (WHO) thermal grade	Thermal damage produced by the electrosurgery **will be graded using the WHO Grading system**. It has 4 grades according to the difficulty in identifying the cellular architecture and, as the grade increases, more is the difficulty in identifying the tissue architecture.	(See **Table 8.** World Health Organization (WHO) thermal grade)
Diagnostic impact	TA has affected to the pathologic diagnosis?	(See **Table 9**)
TA grade in each resected specimen	Grade of TA in each chip obtained from TURBT or in the entire specimen if this is resected *in bloc*.	**Absent**
		Mild: < 25% of the specimen is TA
		Moderate: 25-50% of the specimen is TA
		Severe: >50% of the specimen is TA

Table 8. World Health Organization (WHO) thermal grade

Degree of thermal damage	Characterization
0	No thermal damage
1	Lowest grade of thermal artifacts. The cellular structure is identifiable and not impaired.
2	Medium grade. Cellular structure and nuclei are impaired, but still identifiable
3	High grade artifacts. Complete loss of the cellular structure. No differentiation of the cellular parts.

Table 9. Diagnostic impact of thermal artifact.

Diagnostic impact	Characterization
0	No diagnostic impact
1 (mild)	Difficulty to grade and stage lesion but still possible *without* immunohistochemistry
2 (moderate)	Difficulty to grade and stage lesion but still possible *with* immunohistochemistry
3 (severe)	Inability to grade and stage a lesion

- **TNM staging**

The TNM will be measured according to its last update in 2017 (8th edition). TUR only allows to obtain tissue sample until smooth muscle layer, so we can only diagnose non-muscle-invasive bladder tumors (CIS, Ta, T1) and categorized a tumor as infiltrative if detrusor muscle is invaded (T2a or ≥T2b). T3 or T4 tumors and the presence of lymphatic metastasis ("N") or distant metastasis ("M") need a CT urography to be diagnosed, but this is out of our study. This information will be facilitated by the anatomopathologist

report and also will be important in order to categorize our patients in one of the risk groups. This variable will be measured as a qualitative ordinal variable.

- **Histological grade**

In our study, we will measure the histological grade with the WHO classification of 1973 and the WHO/ISUP classification of 2004/2016. The first one (1973) will allow us to classify the lesions in grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated). The WHO/ISUP classification will permit to us to classify the lesions in:

  - Papillary urothelial neoplasms of low malignant potential
  - Papillary urothelial carcinoma, low grade
  - Papillary urothelial carcinoma, high grade

Patients with lesions diagnosed as papilloma or urothelial proliferation of uncertain malignant potential (papillary hyperplasia) will be excluded of the study because they are not malignant neoplasm.

This information will be facilitated by the anatomopathologist report and also will be important in order to categorize our patients in one of the risk groups. This variable will be measured as a qualitative ordinal variable.

- **Presence of detrusor muscle in the sample**

The presence of detrusor muscle in tissue samples is a quality factor for the transurethral resection, it allows us to stage the lesion adequately, and its presence has shown a lower recurrence rate of non-muscle-invasive bladder tumors.

We will obtain this parameter from the pathologist report. This variable will be measured as a dichotomous nominal qualitative variable (presence of muscle or not)

- **Histological type**

We will obtain this information from the pathologist report. This variable will be measured as a non-dichotomous nominal qualitative variable. Urothelial carcinoma is the most common type in our country, followed by squamous carcinoma and

adenocarcinoma. In our study only pure and classic urothelial carcinomas (100% of urothelial origin) will be considered. Other histological variants will be excluded from the study.

Independent variable:

- **Use of monopolar or bipolar transurethral resection**

This is a qualitative dichotomous variable. It will be expressed by a **percentage of patients** who undergo **monopolar TUR** and patients **who undergo bipolar TUR**. These patients included will have one or several *bladder lesions*, *bigger than 0,5 cm,* with a *papillary morphology highly suspicious of urothelial carcinoma* and will be diagnosed by bladder ultrasounds and cystoscopy. In addition, these patients will be classified in 2 groups according to the **urine cytology** results (**positive** or **negative**) and then, each group will be randomized in two groups: one group will be submitted to monopolar TUR and the other to bipolar TUR. Either monopolar and bipolar TUR are used in this study to diagnose (pathologically) and stage the bladder lesions and to treat patients with non-muscle-invasive bladder cancer [Ta and T1]. Patients with positive urine cytology will undergo TUR and random mucosal biopsies of the bladder (RMBB) (**Figure 12**), because it is recommended in Guidelines due to a higher risk of concomitant carcinoma *in situ*. High grade lesions and infiltrative stages are also related to a positive urine cytology.

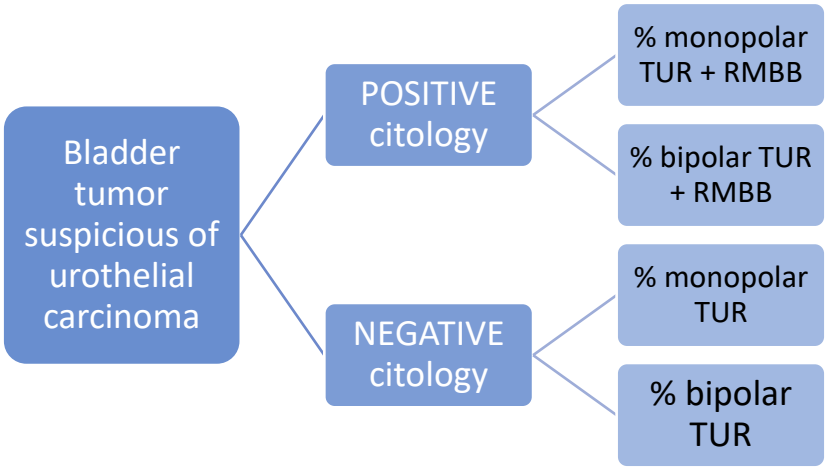


Figure 12. Randomization of patients. TUR= transurethral resection; RMBB= random mucosal biopsies of the bladder.

Covariates:

Table 10. Covariates

Covariate	Type	Measure instrument	Categories or values
Age	Continuous quantitative variable	Clinical examination	≤70 years >70 years
Gender	Dichotomous nominal qualitative variable	Clinical examination	Male Female
Smoking	Dichotomous nominal qualitative variable	Clinical examination	Yes No [1]We will also evaluate the ***pack-year*** index in each patient
Number of tumors	Discrete quantitative variable	Initial cystoscopy and TUR operative report	≥ 1
Type of resection[2]	Dichotomous nominal qualitative variable	TUR operative report	Piecemeal resection *En-bloc* resection
Location	Non-dichotomous nominal qualitative variable	TUR operative report	Vesical neck Trigone Lateral wall Posterior wall Anterior wall
Resection time	Continuous quantitative variable	TUR operative report	Any time[3] (minutes)
Complications during the procedure[4]	Dichotomous nominal qualitative variable	TUR operative report	Yes No

(1) The ***pack-year index*** is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

(2) **Type of resection**. A complete resection is essential to achieve a good prognosis. There are two main types(2):

- **Piecemeal resection in fractions** consists in a separate resection of the exophytic part of the tumor, the underlying bladder wall and the edges of the resection area. This manner is the most used and provides good information about the vertical and horizontal extent of the tumor.
- ***En-bloc* resection** is feasible in selected exophytic tumors, and it provides high-quality resected specimens.

(3) **Resection time**. In this covariate it is important to remark that monopolar TUR has to be performed in less than 1 hour. Nevertheless, bipolar TUR has no limited surgical time.

(4) The **complications** that can occur during TUR are bleeding, obturator nerve reflex, bladder perforation and apparition of TUR syndrome, among others (see *Introduction*, page 25).

8.5 INTERVENTIONS

8.5.1 TRANSURETRAL RESECTION OF THE BLADDER

In our study each urologist and operating surgeon and his/her surgical team must fill out a checklist (***Table 11***), which will be the same for every hospital.

Preoperative period

This part will be evaluated in the initial consultation by the urologist, who will do a detailed history and physical examination (any urinary symptoms, other medical problems and current medications, especially anticoagulants). The urologist should also review the findings from flexible cystoscopy and results of imaging (if they are available). He/she should counsel the patient regarding potential complications, the possible need for biopsy/resection of the prostatic urethra, and the need for postoperative intravesical chemotherapy. In this part, the urologist will offer to the patient the possibility to enter into the study and, if the patient agreed, the informed consent to be added to the study (***Annex 5***) and the informed consent for performing the TUR (***Annex 3***) must be signed.

Preparation in the operating suite

Each patient will have a personal anesthetic strategy (spinal or general anesthetic) considering their comorbidity and the requirement for paralysis. The patients will receive a perioperative antimicrobial prophylaxis. Finally, the urologist will inspect the operating room environment to ensure that the video monitor, camera, range of endoscopes, loops, and biopsy forceps are available. In addition, the surgeon will ensure that the electrocautery modality (monopolar or bipolar) (

Figure 15) is the correct for each patient and, consequently, choose the appropriate irrigating fluid, and that the patient is properly positioned (lithotomy position) (**Figure 16**). A bimanual examination will be performed before and after the procedure.

Operative strategy and intervention

In patients with first diagnosis of BC, the grade and stage will form the cornerstone for future management, so the principal aim of the urologist must be to excise the entire tumor with minimal cautery artifact.

The camera should be white balanced, the energy source set at an appropriate level and the cut setting between 100 and 160 W in general. The urologist will decide the height of the irrigant in order to maintain the bladder at about half capacity during the procedure.

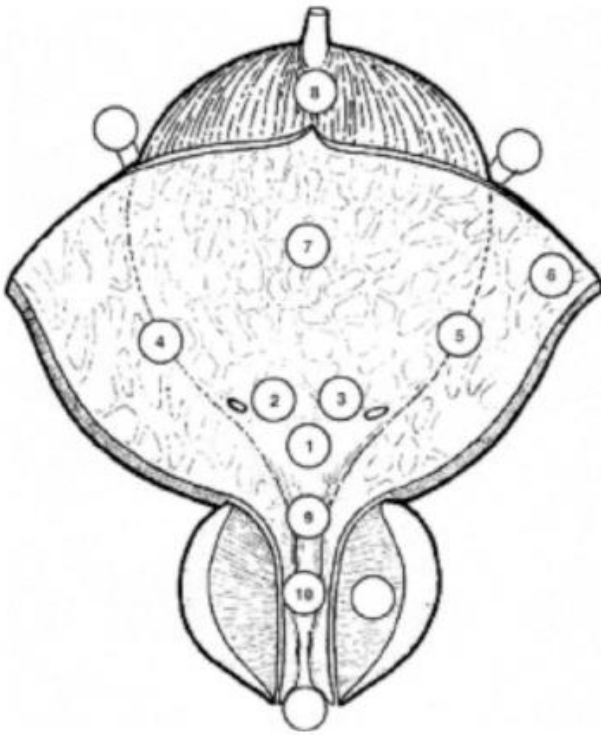


Figure 13. Bladder map. 1= trigone; 2= right ureteral orifice; 3= left ureteral orifice; 4= right wall; 5= left wall; 6= anterior wall; 7= posterior wall; 8= dome; 9= neck; 10= posterior urethra. Extracted from (2).

An initial flexible cystoscopy will be performed to inspect the whole bladder, including a retrograde view of the bladder neck, with the objective of avoiding a false passage. If the endoscope does not pass easily, urethral dilatation will be required. The urethra, prostate and the entire bladder will be inspected, trying to not miss lesions in "blind spots" (bladder dome and anterior bladder neck). The operating surgeon will document the following using a **bladder map** (**Figure 13**): tumor location, shape (solid or papillary), number, and size (reference: resecting loop is 8-10 mm). Enhanced visualization (narrow band or photodynamic "blue-light" diagnosis) will be used to identify additional tumors that may be missed with white light.

For the resection of bladder lesions a resectoscope or resector is used (**Figure 14**, **Figure 15**). This is a complex device equipped with an endoscopic camera, a metal resection loop that uses electric current and an irrigation and fluid drainage channel (use to permit vision and transmit the energy). This intervention is performed endoscopically through the urethra, without abdominal opening. The surgeon inserts the resectoscope under visual control until achieve the bladder. Then, it is possible to remove the lesions and to coagulate the blood vessels susceptible to bleeding (***Figure 18***). There are two main types of resection: *en-bloc* resection (EBRT) and fractionated technique. The principal objective of EBRT is to excise entire tumor and its base in one piece whilst minimizing cautery (***Figure 18***). This technique offers a more accurate staging but has a significant learning curve and is limited by the inability to extract tumors > 3 cm easily. The other technique is the traditional one and it consists in performing the procedure in two stages: separate resection of the exophytic tumor followed by a resection of the tumor base and margins. In both modalities, muscularis propria must be obtained. The samples obtained will be sent to the pathologist for their histological analysis (these will be well identified) together with the bladder map.

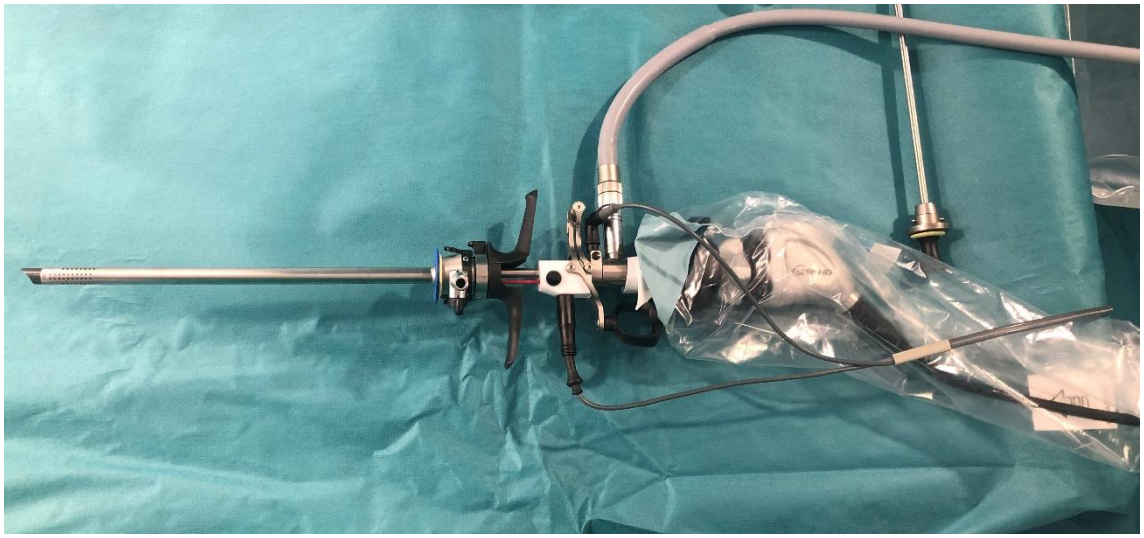


Figure 14. Resectoscope for performing TUR.

In patients with **positive urine cytology** must undergo **random mucosal biopsies** because this finding is related to the presence of concomitant carcinoma *in situ*, so we need to ensure that CIS is not present since this is one of the exclusion criteria. Positive

urine cytology is also related to high grade and infiltrative lesions. These multiple bladder biopsies are taken from the posterior wall, the two lateral walls, the trigone, the bladder dome, and the prostatic urethra (in men).

Postoperative management

A catheter will be inserted to avoid urinary retention and allow for bladder irrigation if needed. Pathologists will report the analysis using a standard protocol (***Annex 1***). In cases where the analysis is limited by the TA or by the no presence of detrusor muscle and HG/T1 tumors, a re-TURBT will be needed (2-6 weeks). Depending on the TUR and pathological results our patients will be include in one of the three risk groups (low, intermediate and high-risk group) and will receive an appropriate management (treatment and follow up) (**Figure 19**).

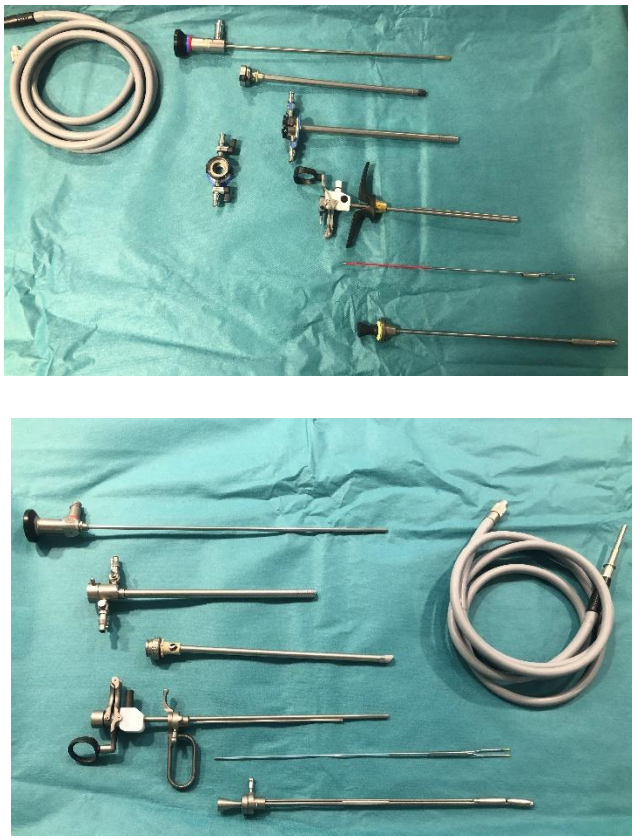


Figure 15. Bipolar (above) and monopolar (below) electrocautery equipments for TUR. From top to bottom the different parts that compose a resectoscope are shown: optic, inner sheath, outer sheath, working element, loop and obturator.

Figure 16. Lithotomy position.

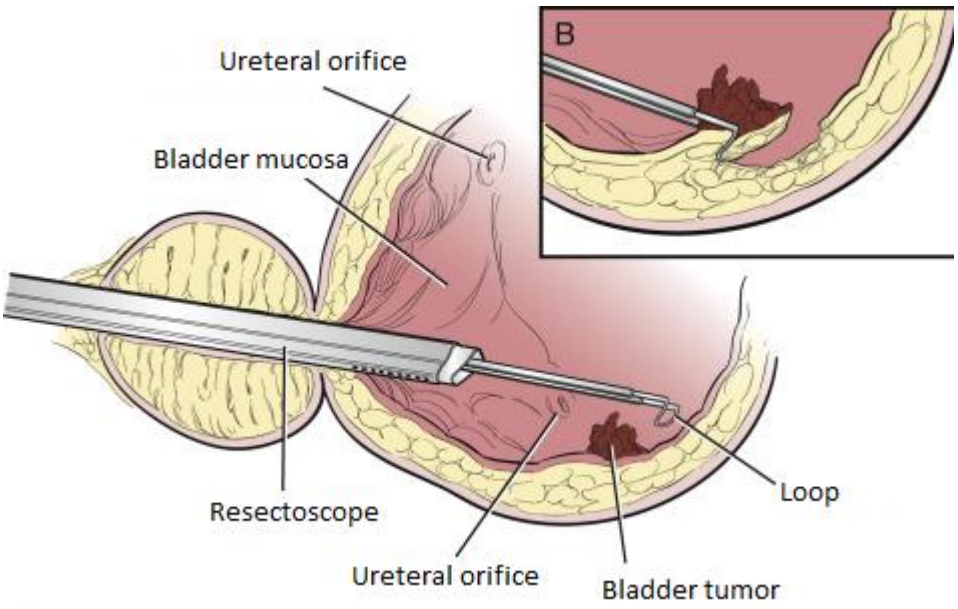


Figure 17. Transurethral resection procedure.

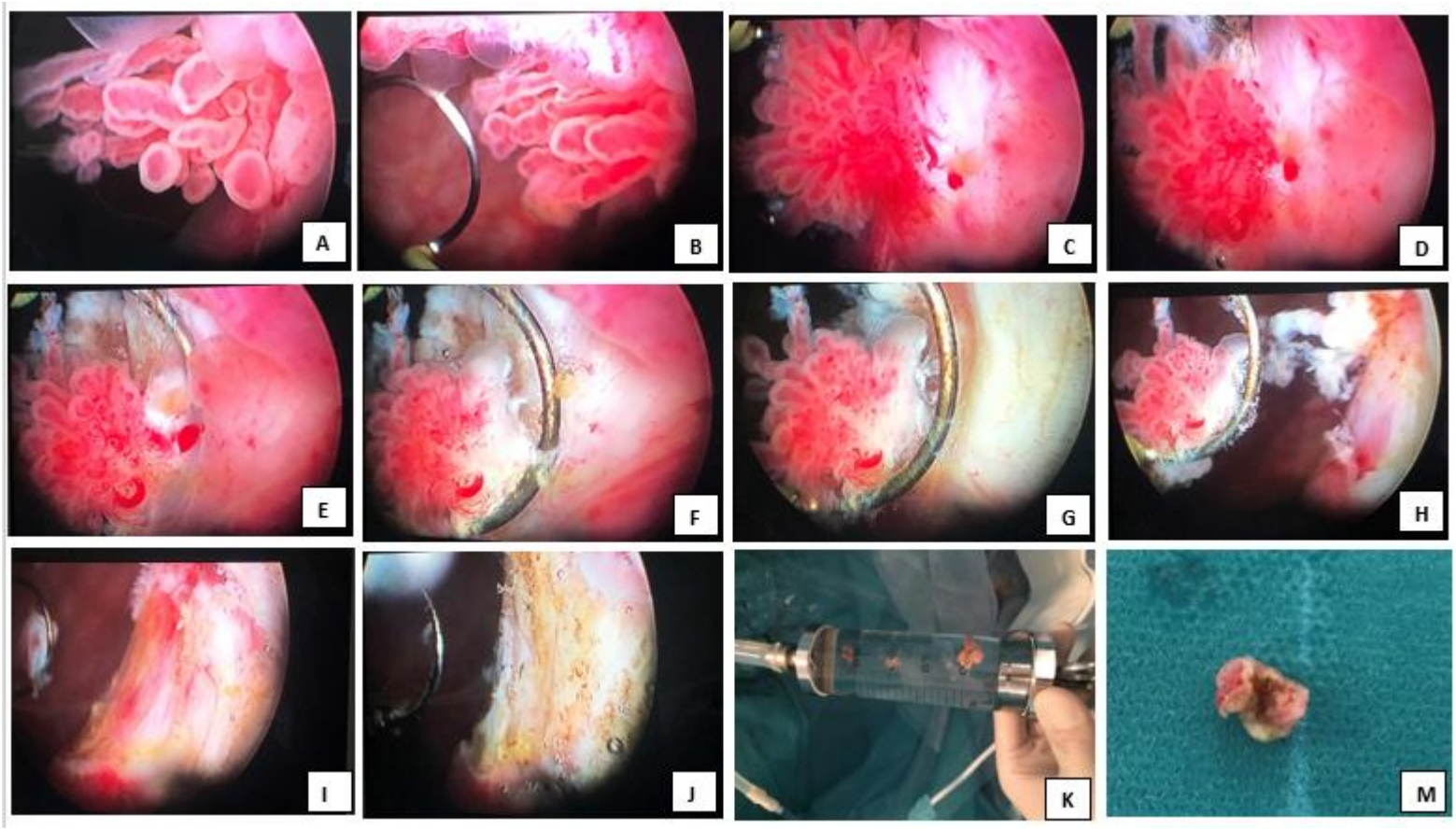


Figure 18. Bladder tumor removal through transurethral resection. Bladder tumor with papillary morphology (A). En-bloc resection with the loop (B-H). Remain superficie without evidence of macroscopic tumor (I). Coagulated remain superficie (J). Presence of muscle in the sample (M).

Table 11. Checklist for the urologists and surgeons.

Preoperative period (Initial consultation and before TURBT)
History and physical examination
Smoking history
Medications (anticoagulants including aspirin)
Cardiac, pulmonary status
Imaging (genitourinary tract) if available
Outpatient cystoscopy information
Cytology results
Consenting the patient with description of the planned procedure, and possible complications and postoperative expectations such as catheterization and intravesical therapy
Review laboratory results
Answer any patient questions
Sign consent (to be added to the study and to perform TUR)
Preparation in the operating room
Discuss the planned anesthesia approach with the anesthesiologist
Decide on preoperative antibiotics
Check the operating room set-up: instruments (sheath, resectoscope, loops, roller if needed, and monopolar/bipolar system), camera, video, strainer, specimen container, and catheter
Decide on irrigation fluid according to the modality assigned: isotonic saline in bipolar electrocautery and glycine in monopolar electrocautery
Operative strategy and intervention
Inspection of entire bladder with cystoscope, included bladder dome and anterior bladder neck
Tumor location, number, size, and appearance (papillary/sessile)
Resection technique (*in bloc* or standard)
Depth and completeness of resection
Visualization of detrusor muscle in the tumor base
Random mucosal biopsies and prostatic urethra if required
Complication, if any
Intravesical therapy if needed
Postoperative period
Pathologist report (***Annex 1***)
Appropriate management (follow-up and treatment)

8.6 DATA COLLECTION AND STUDY CIRCUIT

These three periods described below will be carried out in the 4 selected hospitals at the same time (**Figure 20**). All the data obtained will be collected in a common database that will be later analyzed. A data quality control service will be hired to ensure correct data collection and registration.

Period 1: 1st visit

In the first visit we will see patients who have been previously diagnosed by a urologist with an intravesical lesion (one or several) of papillary morphology and larger than 0.5 cm, highly suggestive of urothelial carcinoma by cystoscopy and ultrasounds.

In this initial consultation we will ask the patient about his entire medical history, and we will do a general and genitourinary physical examination. We will evaluate possible contraindications for performing TUR and certain covariables of the study. In the anamnesis we will ask if they smoke or take any medication, especially anticoagulants. We will ask also about the current process and associated symptoms (hematuria, lower urinary tract symptoms) and about personal and family history of urinary bladder cancer. We will review their recent laboratory tests and cytology results.

Once we have verified that the patient meets all the inclusion criteria and none of the exclusion criteria, we will explain the study and its possible benefits. We will have to explain before signing the informed consent form that there will be a 20% chance of being excluded from the study depending on the anatomopathological findings obtained after TURBT (if it turns out to be T2, other histological variants apart from urothelial carcinoma, concomitant carcinoma *in situ*, or if it turns out to be a papilloma or hyperplasia), but he/she will continue receiving adequate treatment and follow-up despite not continuing in the study. If the patient accepts, he/she will have to sign the informed consent form to be added to the study and also to perform the TURBT. During this visit we must explain the surgical procedure (TUR), its possible complications and the postoperative period (for example, the necessity of catheterization or post-surgery intravesical therapy).

Period 2: TURBT intervention

Patients included in the study will be classified according to the **urinary cytology result**. Those patients with ***positive cytology*** will be randomized into 2 intervention groups: one group will undergo **monopolar TUR** and the other group will undergo **bipolar TUR**. The same will occur with the group of patients with ***negative cytology***. In addition, apart from resecting and sending the lesions to the pathologist for their study, we will evaluate other variables such as the number of tumors, their size, location, etc. The tissue samples obtained will be placed in properly identified containers and sent to the pathologist with additional information (a bladder map (***Figure 13***) with the characteristics of the lesion in the bladder, type of resection, etc.). The pathologist will be blinded for the TURBT modality to avoid bias. The report will indicate the stage of the lesion according to TNM classification, histological grade, presence of thermal artifact, histological type, presence of detrusor muscle in the specimen and lymphovascular invasion. Patients presenting detrusor muscle infiltration (T2), other histological variants apart from pure and classic urothelial carcinoma, presence of concomitant carcinoma *in situ*, or tumors that are papilloma or hyperplasia will be excluded from the study.

The staging and categorization of the histological grade of the tumor by the pathologist and other variables that we will look at during TUR will allow us to classify patients into 3 main risk groups, with different percentages of recurrence and progression and, therefore, with different prognosis. Each of these groups will receive appropriate follow-up and treatment (**Figure 19**).

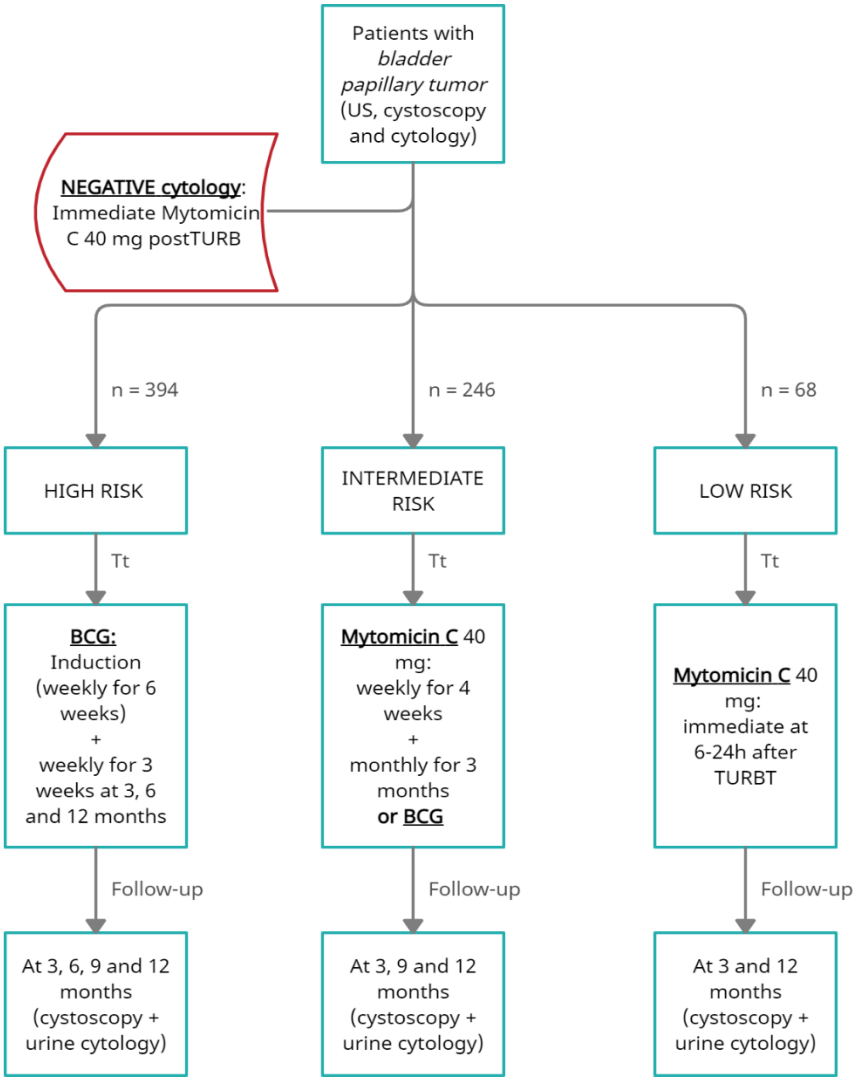


Figure 19. Treatment and follow-up schedule in our study. US= ultrasounds; TURB= transurethral resection of the bladder; Tt= treatment; BCG= Bacilus Calmette-Guérin.

Period 3: treatment and follow-up

We will establish 3 risk groups after performing TUR: low, intermediate and high risk. Each group will receive its corresponding intravesical adjuvant treatment (**Figure 19**). In our study we will apply a follow-up schedule recommended by European Guidelines and EORTC to the 3 risk groups until completing the one-year of follow-up (**Table 3**) (**Figure 19.** Treatment and follow-up schedule in our study. US= ultrasounds; TURB= transurethral resection of the bladder; Tt= treatment; BCG= Bacilus Calmette-Guérin.It

is important to remark that 2 weeks after TURBT a cystoscopy will be performed to confirm that no tumor remains in the bladder. One year after TURBT we will evaluate the percentage of patients who have presented recurrence. These patients will undergo a new TURBT (either monopolar or bipolar) which will indicate what percentage of them have progressed. With this information collected (percentage of patients presenting recurrence and progression at one year post TURB) we will look at what type of TUR modality these patients underwent and what was the degree of thermal artifact found in their tissue samples from the initial transurethral resection.

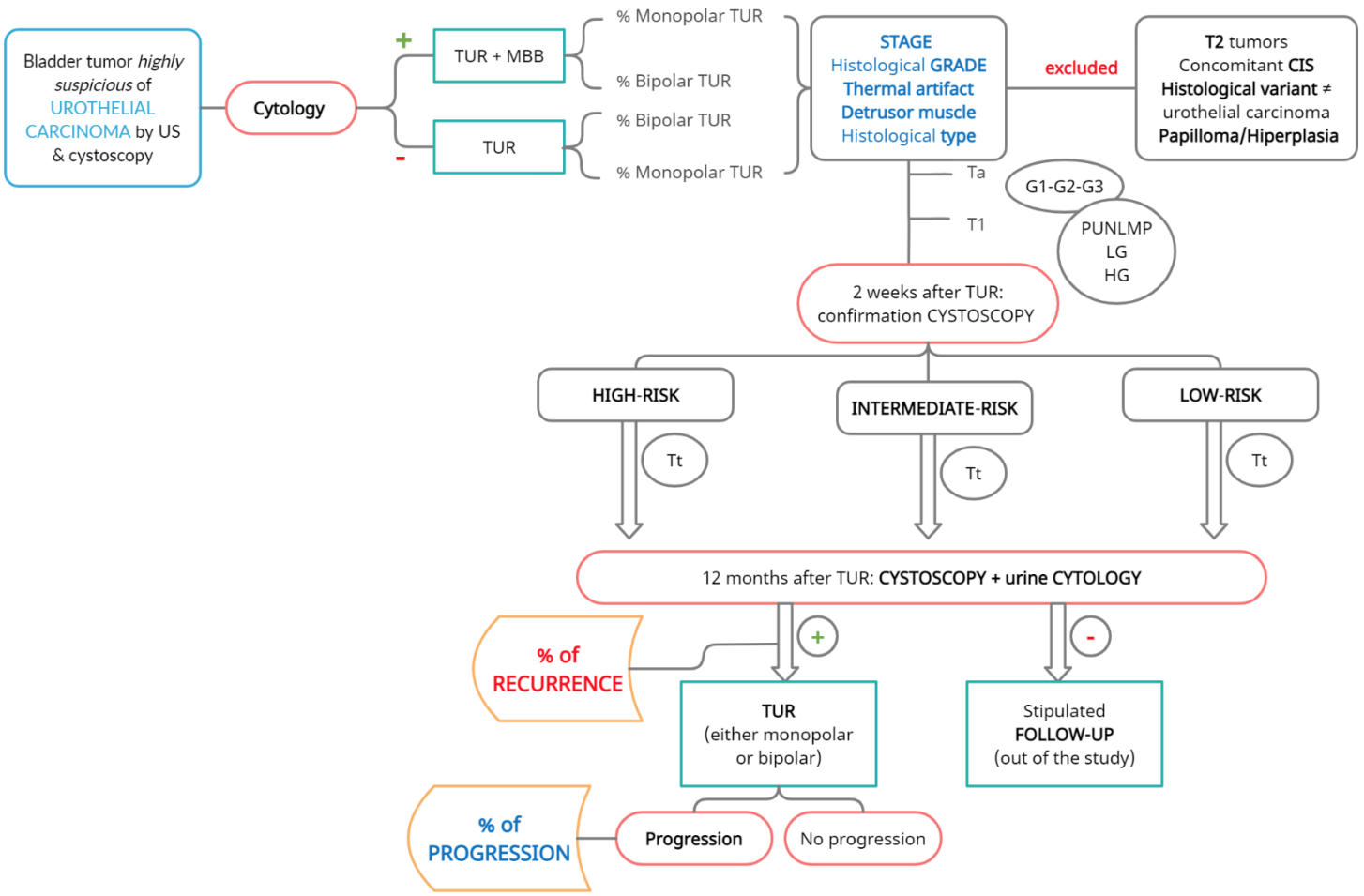


Figure 20. Study diagram. US= ultrasound; TUR= transurethral resection; MBB= multiple bladder biopsies; CIS= carcinoma in situ; PUNLMP= papillary urothelial neoplasm of low malignant potential.

9. STATISTICAL ANALYSIS

All statistical analysis will be performed with Statistical Package for the Social Sciences (SPSS) for Windows ®. Sample size calculation is provided in *Methods* section.

9.1 DESCRIPTIVE ANALYSIS

The dependent variables (recurrence and progression rates, thermal artifact, TNM staging, histological grade, histological type and presence of detrusor muscle) and the qualitative co-variables (gender, smoking, ECOG performance status, Karnofsky index, hematuria, lower urinary tract symptoms, type of resection, location and complications during the procedure) will be summarized by proportions, stratifying by the groups of the independent variable (monopolar or bipolar transurethral resection).

The quantitative co-variables (age, number of tumors, dominant tumor size, no dominant tumors size and the resection time) will be summarized using means and standard deviations (if a normal distribution can be assumed) or medians, first and third quartile (if a normal distribution cannot be assumed), and again stratifying by independent variable groups.

9.2 BIVARIATE ANALYSIS

We will contrast the difference of proportions of the dependent and the qualitative co-variables by the groups of the independent variable, by contrast of a chi-square test or Fisher´s exact test.

Also, we will contrast the difference of means, and of medians for the quantitative co-variables, between the independent groups by the t-Student and the U of Mann-Whitney, respectively.

9.3 MULTIVARIATE ANALYSIS

In addition, multivariate logistic regression analysis will be performed in order to add the covariates that could skew the main association we want to analyze.

We will assume a confidence interval of 95% and P value < 0.05 to consider that there is a significance difference.

10. WORKING PLAN & CHRONOGRAM

RESEARCH TEAM MEMBERS

- Study coordinator: his/her function is to supervise all aspects of the study.
- Urologist: the urologist manager of each hospital. His/her functions are to identify possible candidates and to propose them to enter into the study, and to be in charge of the patients´ follow-up.
- Surgeon: the urologist surgeon in each hospital. His/her function is to carry out all the transurethral resection interventions.
- Two senior pathologists from each hospital. They will be specialized in genitourinary system. They will analyze the tissue samples and will do the histological diagnosis.
- Statistical specialist: to perform the statistical analysis.

STUDY STAGES

The duration of the entire study will be three years and nine months, and it will consist in 5 stages.

Stage 0: Preparation (January 2022 – June 2022)

1. **Protocol elaboration**

   Includes the literature review and all practical considerations to elaborate the protocol (objectives, hypothesis, variables, and methodology).

   Estimated period length: 3 months.

   Responsible to carry out this stage: research team members.

2. **Meeting 1:** participants recruitment and organization

   Includes the selection of the hospitals participating in the study, and its selection of each urologist, surgeon and pathologists. These specialists will evaluate the protocol and decide if they want to participate in the study.

   The research team members (study coordinator, urologist, surgeon and pathologists) of each hospital *will meet once every 6 months* (after the first meeting) to evaluate if the protocol is being well fulfilled. If something does not work, they will take the necessary decisions.

Place of the meeting: Hospital Josep Trueta

3. **Ethics committee´s authorization**

   Presentation of the protocol to the research ethics committee (CEIC) at Hospital Josep Trueta, H. Santa Caterina, H. Vall d´Hebron and H. Clínic. Make any necessary modifications to the protocol, if necessary, to achieve CEIC´s conditions.

   Estimated period length to receive the CEIC authorization: 1 month.

4. **Management department authorization**

   From each hospital participating in the study.

   Estimated period length: 1 month.

5. **Authorization from local government (Generalitat de Catalunya)**

   As it is an invasive procedure in accordance with Spanish legislation (Law 14/2007), it requires authorization from the autonomous community.

   Estimated period length: 1 month.

6. **Training of the researchers**

   The main researchers involved in the intervention or data collection will receive instructions to ensure the maximal and equal adherence to protocol stipulations.

   Estimated period length: 1 month.

Stage 1: Sample collection (July 2022 – September 2023)

1. **Patients' recruitment and randomization**

   The recruitment of patients will last about 1 year and three months. The statistical specialist will design a software for each hospital to carry out the randomization sampling. It will allocate the TUR modality (monopolar or bipolar) to each patient. The patients enrolled in our study must accomplish the inclusion and exclusion criteria and must accept the informed consent.

Stage 2: Intervention, follow-up visits and data collection (August 2022 – October 2024)

1. **Intervention**

   Since the beginning of the recruitment, the patients will undergo TUR (monopolar or bipolar according to the randomization) performing by the urologist surgeon, and the tumor samples will be analyzed by the two seniors pethologists. All the data obtained will be collected in the database.

   Estimated period length: 15 months.

2. **Follow-up visits**

   After transurethral resection, patients will be controlled every 3 months until 1 year in high and intermediate-risk groups, and at 3 months and 12 months after TURBT in low-risk group. Each urologist will record the information collected in every visit in our database. Estimated period length: 12 months for patient (24m)

3. **Construction and control of quality of the data base**

   The database will be revised constantly to guarantee its functioning.

   Estimated period length for data collection and data quality control: 27 months.

Stage 3: Data analysis and interpretation (November 2024 – May 2025)

1. **Statistical analysis**

   It will be performed by an experienced statistical. All the information collected will be analyzed by him or her according to the variables of our trial.

   Estimated period length: 4 months.

2. **Interpretation and elaboration of final report**

   The final article exposing the results of our clinical trial will be written by the study coordinator, in collaboration with the research teams and supervised by the statistical specialist. Estimated period length: 3 months.

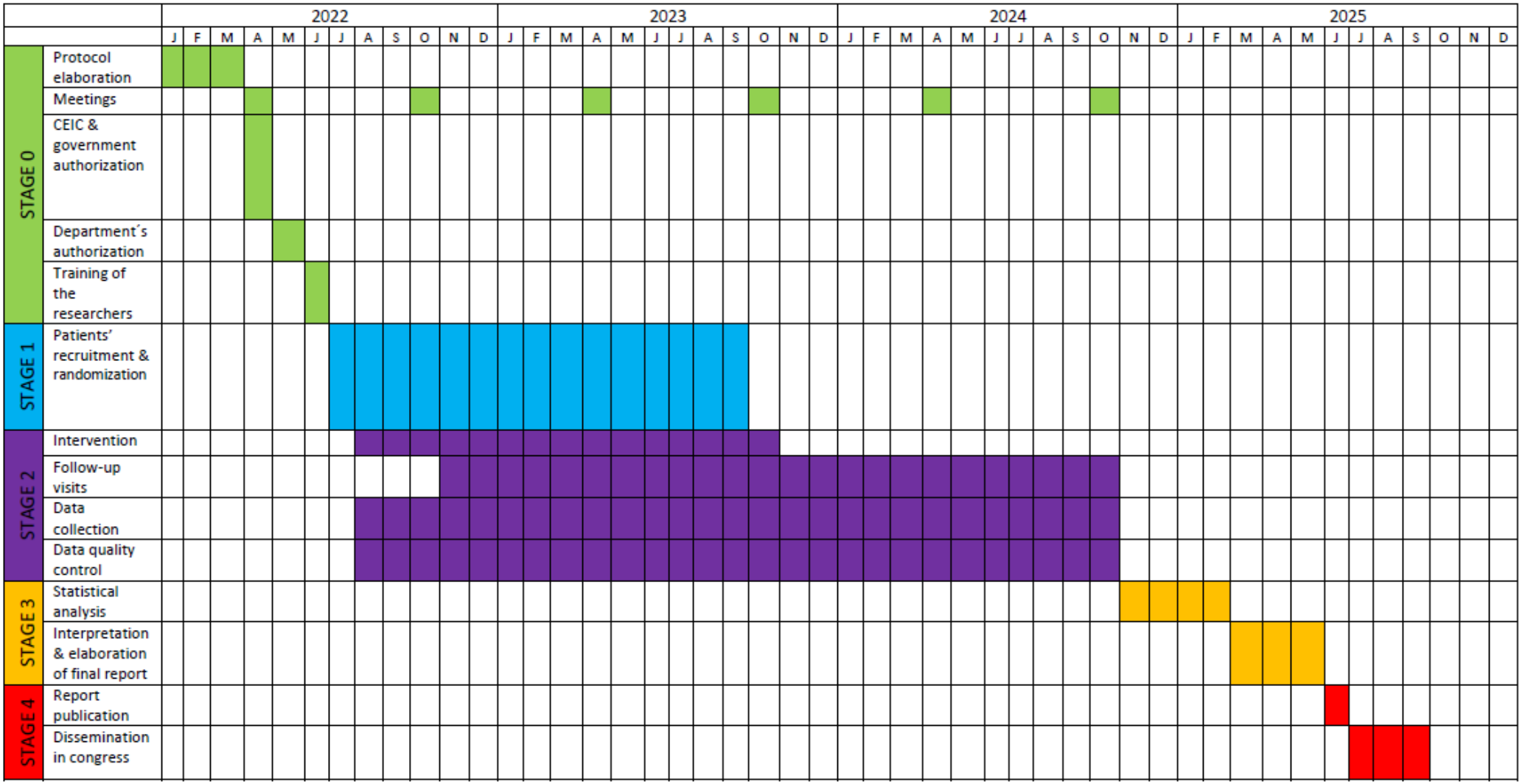
Stage 4: Divulgation (June 2025 – September 2025)

1. **Publication of the results**

   Estimated period length: 1 month.

2. **Dissemination of the results at national and international congresses**

   Estimated period length: 3 months.


2022
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STAGE 0
Protocol elaboration
Meetings
CEIC & government authorization
Department´s authorization
Training of the researchers
STAGE 1
Patients' recruitment & randomization
STAGE 2
Intervention
Follow-up visits
Data collection
Data quality control
STAGE 3
Statistical analysis
Interpretation & elaboration of final report
STAGE 4
Report publication
Dissemination in congress

11. BUDGET

The estimated investment needed to realize our study is 31,220€.

STAFF	
Qualified Statistician: 35€/hour, 120h	4,200€
Study coordinator: 500€/year, 3 years and 5 months	1,700€
Data monitoring and quality control	15,000€
	Subtotal: 20,900€
MEETINGS	
Organization meeting: 40€/person. 13 participants. 1 meeting.	520€
Analyze meetings: 40€/person. 13 participants. 5 meetings.	2,600€
	Subtotal: 3,120€
PUBLICATION	
Paper revision	500€
Paper publication	2,500€
	Subtotal: 3,000€
DISSEMINATION	
Inscription to national congress	300€
Inscription to international congress	500€
Travel accommodation and food, 1700€/participant, 2 participants	3,400€
	Subtotal: 4,200€
TOTAL	**31,220€**

We will hire a biostatistician in order to perform the initial randomization and the statistical analysis of the results. Initially, we have estimated 120 hours of work, with a salary of 35 euros per hour. It would cost 4,200€. In addition, we will need to hire a study coordinator to give assessment and coordinate the medical staff. It would cost 1,700€.

We have assigned 2,500€ for the publication in nation and international journals. For the dissemination at congresses, one national and other international, two researchers will attend with the travel and food included. It corresponds to a total of 4,200€.

Other costs that has not been considered because they are already covered by National Health Care System are salaries of the researchers involved, the procedures (transurethral resections), and the treatments and follow-up visits of the patients participating in our study.

12. ETHICS AND LEGAL CONSIDERATIONS

The study will be performed under the basic ethical principles established by the Helsinki Declaration and the European agreement on Human Rights and Biomedicine (last actualization October 2013) with regards to autonomy, risk-benefit ratio, and protection of vulnerable individuals.

The protocol of the study will be presented to the Clinical Research Ethics Committee (CEIC) of the different centers participating in the study. The committee will ensure that the protocol fits the ethical requirements and any modifications proposed will be implemented into a modified protocol.

The research project will be performed according to the Spanish laws related to clinical trials "Law 14/2007, July 3rd, on biomedical research", which classify our study as an invasive procedure, and related to the basic requirements for the treatment of biological samples of human origin (Royal decree-law 1716/2011, November 18th).

Patients must sign two reports: the first, giving the authorization to perform the intervention (transurethral resection of the bladder); and the second, allowing the participation in our study, after providing comprehensive information.

All personal data collected from each patient during the study will be confidential, only for purpose of research and education. In addition, all data will be analyzed anonymously, in accordance with the present legislation:

- EU Regulation 2016/679 of the European Parliament and the Council of 27 April 2016, in relation to the protection of natural people about processing of personal data and on the free movement of such data.
- Spanish data protection legislation: "Organic Law 3/2018, of December 5, on Data Protection and Guarantee of Digital Rights and the royal decree 1720/2007"

All the investigators will have no conflict of interests. They will also have to agree to publish all data and results with total transparency, including unfavorable data or events.

This study will also adhere to the basic bioethical principles stablished in the Belmont report:

- Autonomy: the recognition that people are autonomous and entitled to their own opinion and choices. In our study, participants will be informed in detail about the study procedures, how data will be handled, and their right to be informed or to withdraw at any moment will be preserved. To express their agreement to participate in the study, they will sign the informed consent form (see Annex). Participant autonomy is regulated through the Spanish legislation: "Law 41/2002, November 14th, regulating patient autonomy and right and obligations of information and clinical documentation".
- Beneficence: is the recognition that people are treated in an ethical manner, respecting their decisions, and protecting them from harm. It is an obligation to secure their well-being. The Belmont report identifies two general rules: do not harm and maximize the benefits. In our study, all participants will be receiving the transurethral resection, the appropriate adjuvant treatment and follow-up. Also, specialists involved will have extensive experience about the matter.
- Non-maleficence: is the obligation of a physician not to harm the patient. In our study, every participant will receive the same diagnosis and therapeutical procedure, and also the same follow-up schedule, that those patients with bladder cancer that do not participate in the study and always following the recommendations of current guidelines.
- Justice: everyone ought to receive the benefits of research. To ensure a just selection of the sample, we have created very inclusive and exclusive criteria, while taking a sample which we consider that would most benefit from this intervention. After sampling, we have randomized the technique elected and the researcher responsible of performing it to ensure equal chances for all participants to receive a specific intervention.

13. STUDY LIMITATIONS

There are some limitations in our protocol which must be taken into account for future analysis and extrapolation of results.

1. This protocol is designed to be applied to those patients newly diagnosed of pure urothelial carcinoma located in the bladder. Recurrent cases, patients with other histological variants or patients with concurrent urothelial carcinomas in other locations of the urinary system will be excluded from the study since they inherently have a worse prognosis. Therefore, this issue limits the study sample and the **target population**. However, if we obtain significant results from our study, in the future more research could be done in these populations.

2. The impossibility of masking the surgeon from the intervention to be performed may lead to a **detection bias**. Nevertheless, to minimize this, the pathologists and the statistical expert in charge of evaluating the results will not know to which group each patient belonged.

3. Being a multicentric trial in which the main intervention is a surgery (operator-dependent) we have to take into account that there is a risk of **variability** in the interventions between different surgical teams. The same occurs with the pathologic analysis. In order to avoid this, all surgeons and pathologists participating in the study will undergo a preparation before the study starts so that everyone can perform the interventions in the same way according to the protocol and they will receive a checklist to perform the same steps for each patient. **One advantage** of being a multicentric study composed by hospitals from several provinces of Catalunya is that, if significant results are achieved, they could be easily more generalized.

4. As the surgery and pathological analysis are operator-dependent, the personal experience and the **learning curve phenomenon** may be an issue that could affect the study results. To avoid these situations, in each hospital the urologist

surgeon will have extensive experience performing TURB and the pathologists will be two seniors specialists in genitourinary system.

5. In a study in which the patient must be followed-up for one year after the intervention (in this case, transurethral resection), there is always a risk of **withdrawals**. To minimize the losses, this possible effect has been taken into account when determining the sample needed for the trial. In addition, there is also the possibility to replace the losses during the recruitment period, as the sampling method in this study is consecutive.

14. IMPACT

Bladder cancer is very frequent in our country, ranking 10th in the world. In our environment, bladder cancer is diagnosed in 75-80% of cases in a non-infiltrating stage, 90% being of urothelial origin. For this reason, it is essential to have an efective tool that helps us to diagnose and treat our patients properly, since if this part of the process is done correctly, the prognosis improves. The main problem with these tumors is that they have a high percentage of recurrence and progression, which varies depending on the assigned risk group. As we have discussed throughout this protocol, there are many factors that may play a role in why these high recurrence and progression rates occur. Some measures have been shown to reduce them, such as the application of adjuvant endovesical treatment.

Transurethral resection of the bladder is the main diagnostic and therapeutic tool in non-muscle-invasive bladder tumors. There are two main electrical modalities, monopolar and bipolar. The first one has been the gold standard for many years until the recent appearance of bipolar energy. The use of the latter has brought many advantages. Among these advantages, some studies have shown that there is less thermal artifact in tissue samples with the use of bipolar energy, which allows a better diagnosis and treatment for our patients. However, nowadays there is still controversy about the magnitude of this thermal artifact when using one modality or the other, and more importantly, whether it has an impact on recurrence and progression rates in patients diagnosed with non-muscle-invasive bladder cancer. As this point is where this trial gets importance, as this is one of the first studies, if not the first, in to evaluate the impact of using monopolar versus bipolar in terms of recurrence and progression rates due to the thermal artifact caused.

Based on our hypothesis, bipolar transurethral resection of the bladder in patients with non-muscle-invasive bladder cancer will cause less thermal artifact in the tissue samples obtained, allowing the pathologist to make a better diagnosis and, consequently, to treat and follow our patient appropriately. This would mean a

reduction in recurrence and progression rates at one year in this group of patients. If confirmed, hospitals will have to take different measures:

- Those hospitals that do not have bipolar energy should invest in a bipolar electrocautery system, or alternatively, refer patients with bladder tumor suspected of urothelial carcinoma to a hospital that has bipolar transurethral resection systems.

This would mean a better management of patients, with a decrease in recurrence and progression rates, and therefore, a better vital prognosis.

15. FEASIBILITY

Medical team

This multicentre study will be done in 4 hospitals from Cataluña. We will have a multidisciplinary team composed by urologists, pathologists, a data manager and a statistical analyst.

These hospitals are:

1. Hospital Universitari Doctor Josep Trueta (Girona)
2. Hospital Santa Caterina (Girona)
3. Hospital Vall d´Hebron (Barcelona)
4. Hospital Clínic (Barcelona)

Necessary means such as personnel salaries, operation rooms, surgical material and follow-ups will be provided by the national health system.

We will hire a data manager to help the investigators at coordinating and data quality control and monitoring respectively, because this multi-center study comprises 4 hospitals. We will need also a statistical specialist in order to statistical analysis, discussion and publication of the results.

Available resources

All the hospitals in the study have weekly operating rooms for the performance of transurethral resection and they have both monopolar and bipolar equipments. The necessary hospitalization for these patients is 2-3 days, so it is important to have beds for these patients after surgery. The material required for this study is the standard material used in the diagnosis, treatment and follow-up of patients with non-muscle-invasive bladder cancer.

Patients

Assuming referral of patients from Hospital Sta Caterina, Hospital Vall d´Hebron, Hospital Clínic, and our own patients from Hospital Universitari Dr. Josep Trueta; we approximate an inclusion in the study of 800 patients per year. So we believe that in about 1 year and 3 months of data collection we will reach our sample size. The follow-up time for the participants will be 1 year more, consequently, thus 2 years and 3 months will be necessary to get the sample size and to evaluate the recurrence and progression rates in patients with NMIBC undergo monopolar or bipolar transurethral resection.

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17. ANNEXES

ANNEX 1: CHECKLIST FOR THE PATHOLOGISTS

ANATOMÍA PATOLÓGICA

CÓDIGO DE IDENTIFICACIÓN DEL PACIENTE

Información recibida por el Departamento de Anatomía Patológica tras la Resección Transuretral:

- Número de tumores vesicales
- Tamaño del/los tumores vesicales
- Localización
- Morfología/ forma de la lesión
- Mapa de la vejiga (con los parámetros anteriores)
- Tipo de resección: en bloque o fraccionada
- Botes con las muestras de tejido tumoral vesical correctamente identificadas

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Información para rellenar por el patólogo:

✓ Estadio de la lesión

☐ Ta ☐ T1 ☐ T2a ☐ T2b ☐ No valorable

Motivo (en caso de no valorable): _____

✓ Grado histológico

OMS 1973: ☐ G1 ☐ G2 ☐ G3 ☐ No valorable

ISUP/OMS 2016:

☐ Papiloma urotelial

☐ Proliferación urotelial de potencial maligno incierto (hiperplasia papilar)

☐ Neoplasia papilar urotelial de bajo potencial maligno (PUNLMP)

☐ Carcinoma papilar urotelial no invasivo de bajo grado (LG)

☐ Carcinoma papilar urotelial no invasivo de alto grado (HG)

☐ No valorable

Motivo (en caso de no valorable): _____

✓ Presencia de capa muscular propia (músculo detrusor)

☐ Sí ☐ No ☐ No valorable

Motivo (en caso de no valorable): _____

✓ Tipo histológico

☐ Urotelial ☐ Escamoso ☐ Adenocarcinoma

☐ Mixto. Especifique: _____ ☐ Otro. Especifique: _____

✓ Invasión linfovascular

☐ Sí ☐ No

✓ Artefacto térmico

- Capa de tejido más afectada:

  ☐ Epitelio ☐ Submucosa (lámina propia) ☐ Muscular

  ☐ No valorable. Motivo: _____

- Grado de artefacto térmico (según la OMS):

  ☐ 0 ☐ 1 ☐ 2 ☐ 3

  ☐ No valorable. Motivo: _____

- Impacto en el diagnóstico (clasificación):

  ☐ 0 ☐ 1 ☐ 2 ☐ 3

  ☐ No valorable. Motivo: _____

- Grado de cauterización en cada pieza obtenida (cada *chip* si resección fraccionada o toda la pieza si resección *en bloque*)

  ☐ Ausente ☐ < 25% ☐ 25-50% ☐ > 50%

  ☐ No valorable. Motivo: _____

ANNEX 2: INFORMATION ABOUT THE INTERVENTION (TRANSURETHRAL RESECTION OF THE BLADDER)

INFORMACIÓN ADJUNTA

Unidad solicitante	Prestación
DT_ Quirófanos Generales	RTU de tumor vesical

HOJA INFORMATIVA SOBRE: INTERVENCIÓN QUIRÚRGICA POR TUMOR DE VEJIGA

Servicio de Urología

Vuestro médico os ha diagnosticado de un tumor vesical. El urólogo os ha propuesto trataros con una intervención quirúrgica para extirpar el tumor, realizando también una biopsia para saber si harán falta tratamientos posteriores.

La intervención quirúrgica se realizará a través del conducto de la orina por Resección Transuretral (RTU) de vejiga.

A continuación, os detallaremos el proceso que se seguirá durante la estancia hospitalaria.

PRIMER DÍA:

1. Ingreso: podréis ingresar el mismo día de la operación. Al llegar al hospital, tendréis que dirigiros al servicio de admisión, donde presentareis la tarjeta sanitaria y os acompañarán al Área Quirúrgica.

2. Preparación para la intervención: la enfermera os pondrá un suero intravenoso y os administrará la medicación preanestésica. También os informará de la hora aproximada en la que os trasladarán al quirófano.

3. Intervención: cuando todo esté preparado se os trasladará a quirófano donde se procederá a la anestesia y posteriormente a la intervención quirúrgica. Los familiares y acompañantes permanecerán en la habitación o la sala de espera del bloque Quirúrgico, donde el urólogo los informará una vez haya acabado la operación.

4. Postoperatorio: antes de entrar a vuestra habitación, os quedaréis unas horas en el área de reanimación postquirúrgica. Llevareis suero con medicación para el control del dolor, y la sonda urinaria conectada a un suero para lavar interiormente la vejiga. Si el lavado por la sonda sale lo suficientemente claro, con la intención de aumentar la eficacia del procedimiento, se administrará un quimioterápico que tiene efecto local.

Durante la noche ya estaréis en vuestra habitación y os podrá acompañar un familiar.

SEGUNDO DÍA:

Después de la valoración del médico, si todo sigue el curso adecuado, al día siguiente de la operación os podremos retirar el lavado vesical.

TERCER DÍA:

El médico os visitará y decidirá si se puede quitar la sonda vesical. Si es así, marcharéis de alta a domicilio cuando hayamos podido objetivar que podéis orinar de manera satisfactoria. Durante unos días notaréis frecuencia y urgencia miccional. En un determinado grupo de pacientes, en ocasiones, es aconsejable que marchéis con sonda vesical y esta sea retirada en el Área Básica de Salud.

Alta hospitalaria

En el informe de alta tendréis anotadas la medicación que tenéis que tomar y la fecha y hora de control de la consulta externa para que os den el resultado de la biopsia.

En caso de prever dificultades en la vuelta al domicilio consulte, previamente al ingreso, con la trabajadora social del área básica de salud/servicio social del ayuntamiento.

No dejéis de comunicarnos si notáis algún tipo de anomalía durante las horas posteriores a la prestación. En caso de urgencia, llamad a la centralita por teléfono para contactar con el servicio de Urología.

Consultad a vuestro médico cualquier duda que tengáis y pedidle más información si lo creéis necesario.

ANNEX 3: TRANSURETRAL RESECTION OF THE BLADDER INFORMED CONSENT

CONSENTIMIENTO INFORMADO

Datos del/la paciente:
Apellidos:
Nombre:
NHC:
Nombres y apellidos de la persona responsable cuando el paciente sea menor o incapaz de dar su consentimiento:
DNI:
Relación con el/la paciente:

Nombre del procedimiento

RTU de tumor vesical

Descripción del procedimiento

Mediante este procedimiento se pretende la eliminación del tejido tumoral de la vejiga y obtener tejido para confirmar el diagnóstico de la lesión.

El médico me ha explicado que el procedimiento requiere la administración de anestesia y que es posible que durante o después de la intervención sea necesaria la utilización de sangre y/o hemoderivados, de los riesgos me informarán los servicios de anestesia y hematología. Mediante esta técnica se extirpan fragmentos de tejido vesical mediante un aparato que se introduce por la uretra, denominado resector, y una fuente de energía que puede ser el electrocauterio o el láser. El medico me ha explicado que la indicación fundamental es el tratamiento de los tumores de vejiga, aunque también puede ser un procedimiento diagnostico para evaluar lesiones sospechosas en vejiga o realizar un control después del tratamiento de tumores vesicales realizando biopsias múltiples.

Comprendo que la resección transuretral de vejiga puede ser un tratamiento quirúrgico único y suficiente en el caso de tumores superficiales de vejiga (con poca infiltración de la pared vesical) y, requiere instilaciones endovesicales posteriores a la cirugía en determinados pacientes dependiendo del estudio anatomopatológico. En caso de tumores vesicales infiltrantes el tratamiento ha de completarse con otros tipos de actuación médica, como cirugía mayor (Cistectomía) o quimioterapia.

El médico me ha dicho que acabada la operación se coloca una sonda vesical.

También me ha indicado que el postoperatorio normal suele ser corto y después se retirará la sonda vesical. Los primeros días es normal notar escozor o sangrado con las primeras micciones, que irán desapareciendo.

Riesgos generales

Cualquier exploración, tratamiento o intervención quirúrgica presenta unos riesgos generales. El riesgo mas grande es la posibilidad de una parada cardiaca. En caso de urgencia vital se ha de actuar sobre estas complicaciones con los medios oportunos por el bien del paciente, de los cuales se le informará (siempre que las circunstancias lo permitan) al paciente o la persona que sea responsable de este.

Riesgos específicos

Cualquier actuación medica tiene riesgos. La mayor parte de las veces los riesgos no se materializan, y la intervención no produce daños o efectos indeseables. Pero es importante que usted conozca los riesgos que puedan aparecer en este proceso o intervención. Comprendo que, a pesar de la adecuada elección de la técnica y de la correcta realización, pueden presentarse efectos indeseables, tanto los comunes derivados de toda intervención y que pueden afectar a todos los órganos y sistemas, como otros específicos del procedimiento como son:

- No conseguir el cese de la hematuria o no poder eliminar la totalidad de la masa tumoral.
- Desarrollar una estenosis uretral que provoque una nueva enfermedad que requiera tratamientos posteriores.
- Incontinencia urinaria que, generalmente es leve, y asociada a urgencia miccional.
- Perforación de víscera vacía durante el acto quirúrgico (recto, intestino, vejiga) y que de suceder esta complicación puede ser necesaria la practica urgente de otra intervención diferente que consistiría en una laparotomía (apertura del abdomen) o en una punción-drenaje, de consecuencias imprevisibles, donde se incluye, aunque remotamente, la posibilidad de muerte.
- Hemorragia incoercible, tanto durante el acto quirúrgico como en el postoperatorio las consecuencias pueden ser muy diversas, dependiendo del tipo de tratamiento que se necesite, y oscilen desde una gravedad mínima hasta la posibilidad cierta de muerte, como consecuencia directa del sangrado o por efectos secundarios de los tratamientos empleados.
- Síndrome de reabsorción de líquidos, a causa del traspaso inevitable del líquido de irrigación al torrente sanguíneo. Este síndrome puede variar desde leve intensidad (amaurosis transitoria, hipotensión…) a gravedad máxima, donde no se puede descartar la posibilidad de muerte.
- Fiebre por infección de la orina y/o de la sangre, de gravedad variable.

- Tromboembolismos venosos profundos o pulmonares la gravedad depende de la intensidad del proceso.
- Hemorragias digestivas que son infrecuentes, pero presentes, a pesar de que se tomen medidas profilácticas y la gravedad depende de la intensidad.

El médico me ha explicado que estas complicaciones habitualmente se resuelven con tratamiento médico (medicamentos, sueros…) pero pueden llegar a requerir una reintervención, generalmente de urgencia, incluyendo un riesgo de mortalidad.

Riesgos más frecuentes: Infecciones urinarias, que son generalmente leves. Hematuria no muy intensa.

Riesgos más graves: Perforación vesical. Sangrado cuantioso, estenosis uretral.

El médico me ha explicado que para la realización de esta técnica puede ser necesaria una preparación previa.

Riesgos personalizados

Ha de informar previamente si tiene alergias a medicamentos y/o contrastes (para evitar su administración durante el procedimiento si se requiriese), toma de antiagregantes o anticoagulantes que pueden aumentar su riesgo de sangrado (atendiendo que se deberían de suspender con suficiente antelación antes del procedimiento, si eso fuese posible), está usted embarazada (para evitar anomalías que puedan dañar al feto).

Otros riesgos personalizados:

Alternativas a la intervención

El médico me ha explicado que otras alternativas son la cirugía abierta o laparoscópica y la quimioterapia, pero que en mi caso la mejor alternativa terapéutica es la RESECCIÓN TRANSURETRAL DE VEJIGA.

Sugerencias del paciente

Autorización

He recibido la suficiente información verbal y/o escrita y he leído la hoja informativa sobre la exploración, anestesia, tratamiento y/o intervención quirúrgica que me harán. He podido hacer preguntas sobre este procedimiento, si así lo creo conveniente. He comprendido la información que se me ha ofrecido, y por tanto, conscientemente autorizo que se lleve a término el procedimiento.

Este consentimiento se formula de acuerdo con lo que establece la Ley 21/2000 de 29 de diciembre.

Servicio solicitante	**Profesional que informa**	**Nº identificación**

UROLOGÍA

Firma y DNI del/la paciente o responsable	Fecha	Firma del profesional

☐ Acepta

☐ No acepta

ANNEX 4. INFORMED SHEET TO PATIENTS ABOUT THE STUDY

HOJA DE INFORMACIÓN SOBRE EL ESTUDIO

Título del estudio: EL USO DE RESECCIÓN TRANSURETRAL MONOPOLAR VERSUS BIPOLAR EN TUMORES VESICALES NO MÚSCULO INVASIVOS CON RELACIÓN AL ARTEFACTO TÉRMICO PRODUCIDO Y LAS TASAS DE RECURRENCIA Y PROGRESIÓN

Investigadora principal: Correa Martín, Naomi

Centros: Servicio de Urología. Hospital Universitario Dr. Josep Trueta (Girona, España), Hospital Santa Caterina (Girona), Hospital Clínic (Barcelona) y Hospital Vall d´Hebron.

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar.

El estudio ha sido aprobado por el Comité Ético de Investigación Clínica del Hospital Universitari de Girona Dr. Josep Trueta, de acuerdo con la legislación vigente, Ley 14/207 del 3 de julio, de investigación biomédica con procedimientos invasivos, y Real Decreto 1716/2011 del 18 de noviembre, en relación con los requerimientos básicos para el tratamiento de muestras biológicas de origen humano.

Nuestra intención es tan solo que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere o no participar en este estudio. Para ello, lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que ello altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

DESCRIPCIÓN DEL ESTUDIO

La resección transuretral de vejiga es un procedimiento quirúrgico mínimamente invasivo que se realiza por vía endoscópica a través del conducto de la uretra y constituye la base del diagnóstico y tratamiento del tumor vesical no músculo invasivo (superficial). En estos casos, normalmente va sucedido de la aplicación de terapia endovesical (quimioterapia o inmunoterapia de acción local), que ha demostrado reducir las tasas de recurrencia y progresión, el principal problema de este tipo de tumores.

Principalmente existen dos modalidades eléctricas de resección transuretral (RTU), monopolar y bipolar, que son las más utilizadas en la práctica clínica habitual y que son el objeto de estudio en este proyecto de investigación. Al resecar el tejido tumoral se crean temperaturas altas que son capaces de cauterizar (quemar) el tejido e impedir un apropiado diagnóstico patológico, que es la base para ofrecer al paciente el tratamiento más adecuado y que éste tenga un mejor pronóstico. La RTU clásica ha utilizado siempre energía monopolar, pero desde hace pocos años la energía bipolar se está utilizando ampliamente en la práctica clínica habitual. Algunos estudios han demostrado que el artefacto térmico que comentábamos antes es menor con el uso de la energía bipolar; sin embargo, otros señalan que es igual al usar una técnica u otra y que no tiene diferente impacto en el análisis histológico. Tampoco, basándose en los estudios que demostraban menor artefacto térmico con el uso de la energía bipolar, se han realizado estudios para objetivar si esto tiene repercusión en las tasas de recurrencia y progresión en pacientes diagnosticados de carcinoma vesical no músculo invasivo.

Por tanto, con el fin de seleccionar la mejor modalidad e implementarla en la práctica clínica hemos diseñado este ensayo clínico donde se someterá de forma aleatoria a pacientes con alta sospecha de carcinoma urotelial vesical a resección transuretral de vejiga con sistema monopolar o bipolar, estudiaremos histológicamente sus muestras para definir el artefacto térmico causado y los seguiremos durante un año para ver cuántos de ellos recurren y progresan. Cuando el seguimiento haya finalizado evaluaremos qué técnica produce más artefacto térmico y su transcendencia en porcentajes de recurrencia y progresión.

Al ser un proceso aleatorizado, todos los pacientes tienen las mismas posibilidades de ser sometidos a una técnica u otra.

PROCEDIMIENTOS DEL ENSAYO

La resección transuretral de vejiga se llevará a cabo en todos aquellos pacientes con lesión tumoral vesical sugestiva de carcinoma urotelial que cumplan todos los criterios de inclusión y ninguno de exclusión. A partir de esta intervención se recogerán varios datos (número de tumores, tamaño de estos, localización, etc.) y las muestras de tejido serán enviadas al Departamento de Anatomía Patológica para ser analizadas: hacer el diagnóstico de confirmación de carcinoma urotelial vesical no músculo invasivo y medir el grado de artefacto térmico, entre otros parámetros.

A las 2 semanas de esta intervención se llevará a cabo una cistoscopia confirmatoria para observar que no queden restos de tejido tumoral dentro de la vejiga.

Finalmente, los pacientes harán seguimiento durante 1 año con cistoscopia y citología urinaria y evaluaremos el porcentaje de aquellos pacientes que recurran, y dentro de estos, el porcentaje de los que progresen.

BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Este estudio pretende ser una referencia para establecer si es más apropiado aplicar una modalidad de resección transuretral de vejiga u otra (energía bipolar o monopolar) en el diagnóstico y tratamiento de pacientes afectos con cáncer de vejiga en estadio no músculo invasivo (superficial), con el objetivo de disminuir al máximo el artefacto térmico causado en las muestras de tejido tumoral, permitir un mejor diagnostico patológico y tratamiento y así intentar reducir las tasas de recurrencia y progresión en este grupo de pacientes.

Se realizarán análisis evaluadores internos durante el transcurso del estudio, para asegurar que no hay diferencias clínicamente relevantes entre los dos grupos de estudio.

La resección transuretral presenta una serie de complicaciones asociadas como cualquier procedimiento invasivo explicados en la hoja de consentimiento informado que usted ha tenido que firmar.

Existe un 20% de posibilidades de ser excluidos del estudio en el transcurso del mismo, después de realizar la resección transuretral y el diagnóstico anatomopatológico. Esto ocurrirá en el caso de pacientes que presenten enfermedad infiltrante, es decir, tumores vesicales que infiltren la capa muscular de la vejiga. Podría pasar porque, aunque en un 75-80% la enfermedad se diagnostica en un estadio inicial, en un 20% de los pacientes ya habrá infiltrado el músculo detrusor y, en estos casos, la primera prueba a realizar será igualmente la resección transuretral con objetivo diagnóstico y no terapéutico. Sin embargo, aunque queden excluidos del estudio, recibirán el tratamiento y seguimiento más adecuado en cada caso.

COMPENSACIÓN ECONÓMICA

Su participación en el estudio no le supondrá ningún gasto. Usted no tendrá que pagar por la resección transuretral, tratamiento y seguimiento, ni recibirá compensación económica.

CONFIDENCIALIDAD

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se ajustará a lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre de protección de datos de carácter personal. De acuerdo con lo que establece la legislación mencionada, usted podrá ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberán dirigirse a su médico del estudio. Los datos recogidos para el estudio estarán identificados mediante un código y solo su médico de estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica.
Sólo se transmitirán a terceros y a otros países los datos recogidos para el estudio que en ningún caso contendrán información que le pueda identificar directamente, como

nombre y apellidos, dirección, número seguridad social, etc. En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito y garantizando la confidencialidad como mínimo con el nivel de protección de la legislación vigente en nuestro país. El acceso a su información personal quedará restringido al médico del estudio/colaboradores, autoridades sanitarias (Agencia Española del Medicamento y Productos Sanitarios), al Comité Ético de Investigación Clínica y personal autorizado por el promotor, cuando lo precisen para comprobar los datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de los mismos de acuerdo con la legislación vigente.

Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos y puede exigir la destrucción de todas las muestras identificables previamente retenidas para evitar la realización de nuevos análisis.

CONTACTO

En caso de cualquier duda durante la realización de este estudio, podrá ponerse en contacto siempre que lo necesite con: _____

ANNEX 5: INFORMED CONSENT TO BE ADDED IN THE STUDY

DOCUMENTO DE CONSENTIMIENTO INFORMADO DEL PACIENTE

Yo, _____, con documento de identificación personal (DNI/NIE) _____ declaro que:

- He recibido una copia de la hoja de información para el paciente.
- He leído y comprendido toda la información que aparece en la hoja de información para el paciente.
- He podido exponer cualquier duda que me ha surgido, y me la han resuelto adecuadamente.
- Estoy conforme con la cantidad de información que me ha sido proporcionada
- Comprendo que mi participación es voluntaria y no remunerada.
- Entiendo los potenciales riesgos y beneficios derivados de participar en este estudio.
- Comprendo que mis datos y pruebas serán confidenciales.

Además, comprendo que aún y haber firmado el consentimiento informado, puedo revocarlo en cualquier momento y que esto no supondrá un perjuicio en mi tratamiento y asistencia sanitaria.

En consecuencia:

- Doy mi conformidad a participar en el estudio "*el uso de resección transuretral monopolar versus bipolar en tumores vesicales no músculo invasivos con relación al artefacto térmico producido y las tasas de recurrencia y progresión*". y estoy de acuerdo en que la información obtenida en este ensayo clínico pueda ser utilizada en investigaciones futuras.
- Acepto que los investigadores del proyecto puedan ponerse en contacto conmigo en un futuro si se considera oportuno.

☐ Sí ☐ No

Firma del paciente **Firma del investigador**

Lugar y fecha: _____, _____ de _____ del año _____

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo, _____, con documento de identificación personal (DNI/NIE) _____ revoco el consentimiento previamente firmado para la participación en el ensayo clínico: "*el uso de resección transuretral monopolar versus bipolar en tumores vesicales no músculo invasivos con relación al artefacto térmico producido y las tasas de recurrencia y progresión*".

Firma del paciente **Firma del investigador**

Lugar y fecha: _____, _____ de _____ del año_____

ANNEX 6: KARNOFSKY INDEX

Puntuación	*Situación clínico-funcional*
100	Normal, sin quejas ni evidencia de enfermedad
90	Capaz de llevar a cabo actividad normal, pero con signos o síntomas leves
80	Actividad normal con esfuerzo, algunos signos y síntomas de enfermedad
70	Capaz de cuidarse, pero incapaz de llevar a cabo actividad normal o trabajo activo
60	Requiere atención ocasional, pero es capaz de satisfacer la mayoría de sus necesidades
50	Necesita ayuda importante y asistencia médica frecuente
40	Incapaz, necesita ayuda y asistencia especiales
30	Totalmente incapaz, necesita hospitalización y tratamiento de soporte activo
20	Muy gravemente enfermo, necesita tratamiento activo
10	Moribundo irreversible
0	Muerto

ANNEX 7. "N" AND "M" OF PATHOLOGIC STAGE CLASSIFICATION OF BC

Table 12. "N" and "M" of Pathologic Stage Classification of urinary bladder carcinoma (2017. 8th Edn.). Adapted from (28).

N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph nodes
M1b	Another distant metastasis