



# Precave: Immediate neoadjuvant instillation of chemotherapy for the prevention of non-muscle invasive bladder carcinoma recurrence: A prospective randomized clinical trial protocol

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## ABSTRACT

**Introduction and objectives:** Recurrence rates for patients presenting with non-muscle invasive bladder carcinoma (NMIBC) can be as high as 60% during the first year after a transurethral resection of bladder tumor (TURBT). Currently, an immediate postoperative instillation of chemotherapy (IPOIC) is recommended for the prevention of recurrences in patients with low to intermediate risk disease. Although in real clinical practice this specific instillation of chemotherapy has many difficulties to be standardized, including its contraindications (suspected or confirmed bladder perforation, wide or extensive resection and, continuous bladder irrigation requirement), which will only make it feasible for around 30% of patients.

We propose in this controlled study, to administer an immediate neoadjuvant instillation of chemotherapy (INAIC), which can be applied technically to all patients, no matter the surgical outcomes and compare it with a control group. We expect to find a reduction in the recurrence rate in the experimental group of at least 15%.

**Methods:** We designed a phase IV, randomized, controlled, open label clinical trial. Main inclusion criteria are: patients with a clinical diagnosis of localized, papillary-type bladder cancer (suspected low to intermediate risk) with a disease-free interval of at least 6 months. Eligible patients will be allocated into group A (INAIC plus TURBT) or group B (TURBT) using a computer-generated block randomization sequence/ratio 1:1. Time to recurrence of both groups will be analyzed and compared using Kaplan-Meier estimates, log-rank tests and, Cox-regression. Univariate and multivariate analyzes will be performed to determine factors which influence recurrence. The study has received the approval of the Ethics Committee for Drug Research (CEIm) of La Paz University Hospital and the Spanish Agency for Medicines and Health Products.

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## 1. Background

### 1.1. Introduction

Bladder carcinoma (BCa) is the seventh most common cancer in the male population and the eleventh most common in women worldwide. The age-standardized incidence rate is 9.0 for men and 2.2 for women [1,2]. In the European Union, the age-standardized incidence rate is 19.1 in men and 4.0 in women [1,2].

Histologically, 90% of bladder tumors are of urothelial origin, 5% are squamous cell carcinomas, and less than 2% are adenocarcinomas or other variants [3].

From all urothelial BCa at presentation, approximately 70% are non-muscle invasive (NMIBC), of these, 70% present in stage Ta, 20% as T1, and 10% as CIS (carcinoma in situ) [4]. These tumors are grouped into the definition of NMIBC, because they can be treated with transurethral resection of bladder tumor (TURBT) and/or intravesical instillations.

To facilitate treatment recommendations, it is important to categorize patients according to risk groups. The standard classification, which is recommended by the European Association of Urology (EAU) guidelines on bladder cancer is based on available

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prognostic factors and in particular data from the EORTC risk tables, and it divides patients into three groups (Table 1).

Depending on the stage and grade, the number and size of tumors, the probability of recurrence of NMIBC can be as high as 60% in the first year and 80% at 5 years after diagnosis. Low-grade Ta tumors have a 50% to 70% recurrence rate, and progress in approximately 5% of cases. In contrast to high-grade T1 tumors that can recur in up to 80%, and progress in up to 50% of patients within 3 years [5–7].

The EAU guidelines recommend the administration of an immediate post-operative instillation of chemotherapy (IPOIC) after TURBT in patients with bladder tumors that are presumed to be NMIBC of low or intermediate risk, that have a low recurrence rate (less than one at one year) and an expected EORTC (European Organization of Research and Treatment of Cancer) recurrence score < 5 (Level of evidence: 1 a. Grade of recommendation: A) [6]. In the United States, the same practice is recommended by the American Urological Association (AUA) guidelines [8].

This recommendation is based on the results of four large meta-analyses which have consistently shown that IPOIC after TURB reduces recurrences compared to TURBT alone [9–12]. On the other hand, contraindications of an IPOIC include: a confirmed or suspected intraperitoneal or extraperitoneal bladder perforation, a wide or extensive resection, or the requirement of continuous intravesical irrigation due to hematuria [6]. Ideally, an IPOIC should be administered within the first 24 hours after surgery (preferably within 2 hours) and it should last for 1–2 hours [6].

Although no comparative studies have been performed between different chemotherapeutic agents, mitomycin C (MMC), epirubicin, and pirarubicin have shown similar beneficial effects [9–12]. Moreover, in addition to an IPOIC, the benefit of continuous irrigation with normal saline has shown efficacy in two meta-analyses [13,14].

The rational explanation for the effectiveness of an IPOIC is based on its antitumor effect in the resection site, in destroying floating cells that can implant further on, and in destroying small tumors that have been overlooked [15,16].

Despite the previous growing evidence that an IPOIC reduces recurrences of NMIBC, many urologists worldwide still do not apply it in their daily practice, due to the fact that in a considerable number of patients (approximately 2 out of 3), the presence of post-operative hematuria or the extent and/or depth of the resection contraindicates this practice [17–19]. So technically, this practice can only be performed in approximately 30% of patients who undergo a TURBT.

Studies which have analyzed the use of an IPOIC have shown that in the United States, only 0.33–45% of patients who underwent a TURBT for suspected NMIBC received it, and that around 66% of urologists do not use it [20–22]. Meanwhile, in 5 European

countries (Germany, Spain, France, Italy, United Kingdom), only 56.7% of patients received it, and 28% of urologists do not use it [23]. In the previously mentioned studies, authors describe possible justifications for not performing this routine practice, such as: problems with low reimbursement, difficulties in preparing chemotherapy drugs and delivering them to the operating room on time, lack of organization, insufficient training of the nursing staff in the use of chemotherapy, among others [20–23]. Furthermore, the lack of scientific evidence of its usefulness in intermediate and high-risk tumors may contribute to the non-compliance of this step in the treatment of NMIBC.

The role of an immediate neoadjuvant instillation of chemotherapy (INAIC) has not been studied other than in a prospective, randomized clinical trial using an electromotive drug administration device (EMDA) with MMC [24]. In this study published by Di Stasi in 2011, it was found that patients who received neoadjuvant MMC with EMDA experienced a longer disease-free interval compared to TURBT alone, and TURB plus IPOIC: 51 months versus 16 months versus 12 months ( $P < 0.001$ ) [24]. Although no data on progression or disease specific survival were included, these findings are promising for the use of a neoadjuvant instillation of chemotherapy.

At the beginning, this clinical trial was intended to use only Mitomycin C as the only chemotherapeutic agent, but due to the stock break and shortage in Spain at the end of 2019, we have decided to propose the use of other drugs with the same indication and evidence that justifies its use in this disease (Epirubicin, Adriamycin, Cisplatin, Gemcitabine, Docetaxel). All the drugs mentioned before are authorized for use in intravesical instillations for the prevention of recurrences of urothelial bladder carcinoma, just like Mitomycin C, and none has shown superiority over another in clinical trials [6,25–29]. Every effort will be made to avoid excessive diversification between drugs and use Mitomycin C, Gemcitabine or Epirubicin whenever possible.

In this study we propose to carry out an intravesical instillation of chemotherapy in a neoadjuvant way (INAIC), that is, immediately before TURBT. If it were effective in prolonging disease-free intervals and reducing the recurrence rate, its use in urology departments would be easily adopted and it could benefit patients regardless of the extension and depth of the TURBT.

In any case, the administration, or not, of neoadjuvant chemotherapy will not influence the subsequent surgical treatment and the procedures in the follow-up of the patient in this clinical trial, which will be carried out according to the usual clinical practice, based on the risk groups.

## 1.2. Rationale

If there is a considerable number of patients who will not be able to receive an IPOIC due to the previous mentioned contraindications and lack of use in clinical practice by urologists worldwide due to its complexity, it will not help to prolong their disease-free intervals. In this scenario, we should come out with a novel strategy, in which potentially all patients can benefit from chemotherapy.

In the light of this conclusion, we decide to create a randomized, open label, controlled trial, comparing the use of INAIC before TURB and compare the disease-free intervals with a control group. A protocol or results from a similar study have not been published in the medical literature so far.

Based on the evidence, we hypothesize that neoadjuvant chemotherapy may act on neoformative foci not visible due to their size during TURBT and may also reduce the possibility of tumor cell implantation by weakening floating tumor cells.

**Table 1**

Non-muscle invasive bladder cancer risk group stratification (adapted from Babjuk M, et al. EAU Guidelines: Non-muscle-invasive Bladder Cancer 2020 [6]).

Risk group stratification	Low-risk	Intermediate-risk	High-risk
Characteristics	Primary, solitary, TaG1 (PUNLMP, LG), <3 cm, no CIS	All tumors not defined in other categories	Any of the following: -T1, G3 (HG), -CIS, -Multiple, recurrent, and large (>3cm) TaG1-G2/LG

PUNLMP: Papillary urothelial neoplasm of low malignant potential; LG: low grade (includes G1 and some forms of G2); G: high grade (includes some G2 and all G3).

## 2. Methods and analysis

### 2.1. Study design: clinical trial, phase IV, randomized, open label, controlled

#### 2.1.1. Study arms

- Experimental: A Intervention: patients will receive an intravesical instillation of neoadjuvant chemotherapy (40 mg of MMC dissolved in 40 ml of normal saline) and immediately afterwards, TURBT will be performed.
- Control group: B Intervention: TURBT

#### 2.1.2. Follow-up

Patients in both arms will be followed-up according to standard clinical practice according to the guidelines established in our service: first cystoscopy and urine cytology at 3 months. Subsequently, the follow-up will be done according to the recommendations of the EAU guidelines [6].

We define early recurrence as a reappearance of the bladder tumor in the first 12 months after resection.

The subsequent treatment of NMIBC will be carried out according to the guidelines established in our service, regardless of the treatment group to which it has been assigned. Thus, intermediate-risk patients will be given intravesical prophylaxis treatment with MMC at a schedule of 40 mg weekly for the first 4 weeks (starting 2 weeks after TURB) followed by a monthly administration of 40 mg for 11 months.

#### 2.1.3. Place of realization

We have started the study at the La Paz University Hospital in Madrid. Currently other centers who collaborate with the Club Urológico Español de Tratamiento Oncológico (CUETO) in Spain have decided to collaborate and are under the process of becoming approved enrollment centers.

### 2.2. Eligibility criteria

Inclusion and exclusion criteria are summarized in Table 2:

### 2.3. Interventions

Patients randomized in the intervention group (Group A) will receive an INAIC through a 16Fr Foley catheter for 15 minutes right after the induction of anesthesia and prior to TURBT. The preferred agent for INAIC will be MMC 40 mg. In case that MMC is not

**Table 2**  
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Both sexes, $\geq 18$ years old, clinical and/or imaging evidence of localized papillary-type BCa with indication for TURBT.	Solid-looking or muscle-invasive tumors on cystoscopy and/or preoperative imaging tests
History of NMIBC: Ta / T1, G1-G3, without CIS, with disease-free interval > 6 months	Allergy to intravesical administered chemotherapeutic agents
Karnofsky scale score > 70%.	Pregnancy
Agreement of the patient to participate, signed informed consent.	Severe urethral stricture/stenosis or inability to catheterize the bladder for any other reason prior to TURBT
	Patients in whom follow-up will not be possible for any reason.
	Final diagnosis different from that of Ta-T1 tumors

BCa: Bladder carcinoma; TURBT: transurethral bladder resection of bladder tumor; CIS: carcinoma in situ.

available at the pharmacy, other approved agents are Epirubicin, Gemcitabine, Adriamycin, Cisplatin and, Docetaxel.

### 2.4. Aims and objectives

#### Primary Objective:

- Evaluation of the early recurrence rate (<12 months) of NMIBC comparing both study arms.

#### Secondary Objectives:

- Evaluation of toxicity, adverse events and complications attributable to intravesical instillation of chemotherapy prior to TURBT.
- Determine the late recurrence rate (12–60 months).
- Compare the recurrence-free interval between both groups.
- Determine clinical and demographic variables that could influence clinical response.
- Determine differences in rate of recurrence, adverse effects and other variables between patients in the intervention group who have received different drugs.

### 2.5. Sample size

The sample size is calculated to find a reduction of 15% in group A (INAIC + TURB) over group B (TURB alone), assuming that the recurrence rate in group B is 60%. A total of 120 patients will be required in each group, with a probability of 80% and a 5% type 1 error.

### 2.6. Allocation

Patients will be assigned to 1 of the 2 groups using a computer-generated block randomization sequence. Participants will be intentionally placed in equal numbers to each group (A or B) according to a block of 4 (randomization ratio 1: 1 in each block). The randomization process will take place when the exact day and time of surgery is known (approximately 1 to 2 weeks prior to surgery).

### 2.7. Data collection

At the time of registration, each patient will be assigned a Patient Number. This Patient Number will be noted on the electronic medical record and in the database. The researcher will be responsible for keeping adequate information about each patient so that health authorities can have access to such information if necessary. These records must be kept confidential during the period of time legally ordered by current regulations.

The documentation related to the study (protocol, database, signed informed consents, authorizations, etc) will be stored in the Urology Department at La Paz University Hospital in a safe place and easily accessible by the research team. All information contained in clinical, histological, biochemical, and molecular reports, observations, or other activities is necessary for the reconstruction and evaluation of the study.

### 2.8. Timeline

The study started on May 2018, after obtaining the approval of the study by the Ethics Committee for Drug Research (CEIm) of the Hospital Universitario La Paz and the Spanish Agency for Medicines and Health Products (AEMPS).

The study is intended to be carried out according to the following work plan:

- Duration of the recruitment period: 36 months.
- Duration of the follow-up period for each patient: 5 years.
- Analysis of the results and preparation of the final report: 3 months.
- End of study: last scheduled visit of the last patient in the study.

## 2.9. Quality control

The study will be monitored by a monitor, who will draw up a suitable monitoring plan for the study. Regular visits and phone calls will be made to investigators. The monitor should evaluate the study procedures and discuss any problems with the investigator. During the course of the study, audit visits may be carried out at the participating centers.

## 2.10. Data analysis plan

The qualitative variables will be analyzed in 2x2 tables, they will be compared using the  $\chi^2$  (Chi-square) test.

Main variable: The time to the recurrence of NIMCV will be analyzed between both groups using Kaplan-Meier estimates, log-rank test and Cox regression. The recurrence rate per year will be defined as the total number of recurrences confirmed by pathological analysis divided by the number of years of follow-up. The recurrence rate per year between the two groups will be compared by Fisher's exact test or Student's t test.

Secondary variables: Univariate and multivariate analyzes will be performed to determine the factors that affect recurrence.

Two homogeneous groups will be generated (Group A and B) avoiding conformational biases (selection bias, attrition bias), through statistical analysis by intention to treat/stratified blocks, considering risk factors for recurrence (low and intermediate) based on in the latest reviews of scientific literature: sex, age, smoking history, American Society of Anesthesiologists (ASA) classification system status, Charlson Comorbidity Index (CCI), tumor size, number of tumors, urinary cytology, history of previous NMIBC, history of previous intravesical chemotherapy treatment, adverse effects, surgical complications.

In order to minimize information biases (detection, confusion), multivariate analysis techniques will be used. In all the analyzes, a significance level (p) will be established at values below 0.05, that is, a 95% confidence interval.

## 3. Ethics and dissemination

The treatment, communication and transfer of the personal data of all the participating subjects will comply with the provisions of the Spanish Organic Law 15/1999, of December 13, on the protection of personal data.

The study will be carried out in accordance with the recommendations for clinical studies and drug evaluation in humans, which appear in the latest version of the Declaration of Helsinki (Fortaleza, Brazil October 2013, Annex 3), revised in successive world assemblies, and the current Spanish Legislation on Clinical Studies (RD 1090/2015, of December 4, which regulates clinical trials with drugs).

## 4. Trial registration number and approval

This trial was approved by the Spanish agency of Medicines and Medical Devices (AEMPS) with the trial number: EudraCT 2017-004070-34. First approved: January 29th 2018. Last protocol version: 3.0 May 12th 2020.

Title of the clinical trial in Spanish: "Instilación vesical de quimioterapia previa a la resección transuretral de vejiga en el tratamiento del cáncer de vejiga".

Link to the registration (must be publicly accessible): <https://reec.aemps.es/reec/public/list.html>

## Author contributions

DMC and LMP wrote the first draft of the manuscript. DMC, JGR, CBR, MAM, FRB, AAB and LMP contributed to the conception and design of the study and, acquisition of data, critical revision of the manuscript, and final approval of the version to be submitted.

## Ethical approval

This clinical trial was approved by the Institutional Review Board and Ethics Committee at La Paz University Hospital, Madrid, Spain on December 22nd 2017 with the code: HULP:4963.

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## Guarantor

None.

## Research registration number

None.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Trial registration data:

Data category	Information
Primary registry and trial identification number	EudraCT 2017-004070-34
Protocol code	PRECAVE
Date of authorization in primary registry	January 29th 2018
Sources of monetary or financial support	Supported by grants from the Foundation for Research in Urology (Spanish Urological Association) and from the Community of Madrid (Immunothercan-CM(B2017/BM D3733))
Sponsor	Dr. Luis Martínez-Piñero Lorenzo – Urology Department, La Paz University Hospital, Madrid, Spain
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## Trail registration data: (continued)

Data category	Information
Study type	Phase IV, randomized, open label, controlled
Public title	Instilación vesical de quimioterapia previa a la resección transuretral de vejiga en el tratamiento del cáncer de vejiga
Scientific title	Ensayo clínico aleatorizado, abierto para evaluar la instilación vesical de quimioterapia neoadyuvante a la resección transuretral de vejiga para la prevención de recurrencia del carcinoma urotelial no músculo invasivo
Countries of recruitment	Spain
Interventions	Group A: instillation of intravesical chemotherapy immediately prior to TURBT. Group B: control
Date of first patient enrolled	May 29th 2018
Recruitment status	Patient enrollment ongoing
Key inclusion criteria	Age $\geq$ 18 years, any gender Localized, papillary-type, bladder carcinoma Disease free interval > 6 months (only Ta/T1, G1/G3, without CIS)
Key exclusion criteria	Solid or muscle invasive tumors Allergy to intravesical chemotherapeutic agents Pregnancy Any reason for not being able to catheterize the bladder prior to surgery
Primary outcome	Evaluate early recurrence rate (<12 months)
Secondary outcomes	Evaluate toxicity, adverse events and complications Determine late recurrence rate (12–60) Determine the late recurrence rate (12–60 months) Compare the recurrence-free interval Determine clinical and demographic variables that could influence clinical response Determine differences in rate of recurrence, adverse effects and other variables between patients in the intervention group who have received different drugs

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