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Original Article

VI-RADS followed by Photodynamic Transurethral Resection of Non-Muscle-Invasive Bladder Cancer vs White-Light Conventional and Second-resection: the 'CUT-*less*' Randomised Trial Protocol

Francesco Del Giudice[1,2,3], Annarita Vestri[4], Danilo Alunni Fegatelli[5], Tanja Hüsch[6,7], Jonathan Belsey[8], Rajesh Nair[3], Eila C. Skinner[2], Benjamin I. Chung[2], Martina Pecoraro[9], Alessandro Sciarra[1], Giorgio Franco[1], Benjamin Pradere[10], Paola Gazzaniga[11], Fabio Massimo Magloicca[9], Valeria Panebianco[9] and Ettore De Berardinis[1]

[1]*Department of Maternal Infant and Urologic Sciences, "Sapienza" University of Rome, Policlinico Umberto I Hospital, Rome, Italy,* [2]*Department of Urology, Stanford University School of Medicine, Stanford, CA, USA,* [3]*Guy's and St. Thomas' NHS Foundation Trust, Guys Hospital, London, UK,* [4]*Department of Public Health and Infectious Disease, "Sapienza" University of Rome,* [5]*Department of Life Sciences, Health and Health Professions, Link Campus University, Rome, Italy,* [6]*Clinical development and Medical Affairs, Photocure, ASA, Oslo, Norway,* [7]*Department of Urology and Paediatric Urology, University Medical Centre of Johannes-Gutenberg University, Mainz, Germany,* [8]*JB Medical Ltd, London, UK,* [9]*Department of Radiology, Oncology and Pathology, "Sapienza" University of Rome, Policlinico Umberto I Hospital, Rome, Italy,* [10]*Department of Urology, La Croix Du Sud Hospital, Quint Fonsegrives, France, and* [11]*Department of Molecular Medicine, "Liquid Biopsy" Unit, "Sapienza" University of Rome, Policlinico Umberto I Hospital, Rome, Italy*

Background

A second transurethral resection of bladder tumour (Re-TURBT) is recommended by European Association of Urology (EAU) Guidelines on non-muscle-invasive bladder cancers (NMIBCs) due to the risk of understaging and/or persistent disease following the primary resection. However, in many cases this may be unnecessary, potentially harmful, and significantly expensive constituting overtreatment. The CUT-*less* trial aims to combine the preoperative staging accuracy of Vesical Imaging-Reporting and Data System (VI-RADS) and the intraoperative enhanced ability of photodynamic diagnosis (PDD) to overcome the primary TURBT pitfalls thus potentially re-defining criteria for Re-TURBT indications.

Study Design

Single-centre, non-inferiority, phase IV, open-label, randomised controlled trial with 1:1 ratio.

Endpoints

The primary endpoint is short-term BC recurrence between the study arms to assess whether patients preoperatively categorised as VI-RADS Score 1 and/or Score 2 (i.e., very-low and low likelihood of MIBC) could safely avoid Re-TURBT by undergoing primary PDD-TURBT. Secondary endpoints include mid- and long-term BC recurrences and progression (i–ii). Also, health-related quality of life (HRQoL) outcomes (iii) and health-economic cost–benefit analysis (iv) will be performed.

Patients and Methods

All patients will undergo preoperative Multiparametric Magnetic Resonance Imaging of the bladder with VI-RADS score determination. A total of 327 patients with intermediate-/high-risk NMIBCs, candidate for Re-TURBT according to EAU Guidelines, will be enrolled over a 3-year period. Participants will be randomised (1:1 ratio) to either standard of care (SoC), comprising primary white-light (WL) TURBT followed by second WL Re-TURBT; or the Experimental arm, comprising primary PDD-TURBT and omitting Re-TURBT. Both groups will receive adjuvant intravesical therapy and surveillance according to risk-adjusted schedules. Measure of the primary outcome will be the relative proportion of BC recurrences between the SoC and Experimental arms within 4.5 months (i.e., any 'early' recurrence detected at first follow-up cystoscopy). Secondary outcomes measures will be the relative proportion of late BC recurrences and/or BC progression detected after 4.5 months follow-up. Additionally, we will compute the HRQoL variation from NMIBC questionnaires modelled over a patient lifetime horizon and the health-economic analyses including a short-term

cost–benefit assessment of incremental costs per Re-TURBT avoided and a longer-term cost-utility per quality-adjusted life year gained using 2-year clinical outcomes to drive a lifetime model across the two arms of treatment.

Trial Registration

ClinicalTrial.gov identifier (ID): NCT05962541; European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) ID: 2023-507307-64-00.

Keywords

non-muscle-invasive bladder cancer, photodynamic diagnosis, blue-light cystoscopy, transurethral resection of bladder tumour (TURBT), Re-TURBT, Vesical Imaging-Reporting and Data System, multiparametric magnetic resonance imaging

Background

The prevalence and incidence of bladder cancer (BC) across the European Union (EU) constitutes a major healthcare concern. BC is the sixth leading cause of cancer in the EU, with 124 000 diagnosed and >40 000 dying from the disease each year, accounting for a major cost burden across all healthcare systems [1–3]. By 2030 the annual incidence of BC is projected to increase to 219 000 cases, with two-fifths of this increase attributed to the increasing overall age of the European population [4]. Notably, the vast majority (75–80%) of patients with BC present with disease confined either to the mucosa (Stage Ta, carcinoma *in situ* [CIS]) or the submucosa (Stage T1) according to the TNM classification system [5], differently from the less common, but significantly more deadly muscle-invasive BCs (MIBCs; Stage T2–T4).

The initial surgical management of both non-MIBC (NMIBC) and MIBC is transurethral resection of bladder tumour (TURBT). However, there are many potential issues that can affect TURBT performance, including a high degree of operator dependence for optimal outcomes [6,7]. Along these lines, one particular issue is that many of the so-called early BC recurrences are actually incomplete resections during primary TURBT [8]. Inadequate resections can also lead to understaging (i.e., inaccurate discrimination between NMIBC and MIBC), which can adversely affect survival. In particular, incomplete tumour resection rates vary between 33% and 76% for all cases, with 27–72% and 33–78% for Ta and T1 tumours, respectively. More importantly, underestimation of tumour depth of invasion at first TURBT has been demonstrated in up to 7–30% of cases, increasing up to 45–51% in those with T1 tumours where no detrusor muscle was sampled in the specimen after initial TURBT [9,10].

Accordingly, European Association of Urology (EAU) Guidelines recommend a second-look and resection (i.e., Re-TURBT) 2–6 weeks after the primary TURBT in cases of (i) incomplete initial TURBT or doubt about completeness of a TURBT, (ii) if there is no detrusor muscle in the specimen after initial TURBT, and (iii) in all T1 tumours [11].

As such, Re-TURBT has been advocated as an 'emergency rescue' performed because of the quality issues intrinsically inherent to the initial TURBT (i.e., the relatively low radicality and the low staging sensitivity). However, this can result in significant detriments to the patient's quality of life (QoL) (e.g., second hospitalisation, potential risk for complications, delay in definitive treatment etc.) or additional negative social implications (e.g., productivity loss, indirect costs etc.) and healthcare-related costs (e.g., surgical procedure costs, in-hospital recovery costs, postoperative care etc.).

The 'CUT-*less*' trial will evaluate the possibility for safely omitting secondary resections by combining the advantages of preoperative multiparametric MRI (mpMRI) accuracy and the visually-enhanced features of PDD during the primary resection.

A mpMRI of the bladder offers indeed, on one hand, an opportunity to reduce staging errors through better anatomical visualisation [12,13]. Along these lines, the Vesical Imaging-Reporting and Data System (VI-RADS) has been introduced to develop a systematic approach to report bladder MRI results and to define the risk of muscle invasiveness and clinical T stage (cT) [14]. In this setting, VI-RADS has been worldwide validated as an accurate and reliable diagnostic tool for preoperative BC staging [15,16]. Additionally, there is a growing body of evidence exploring the utility of VI-RADS into clinical applications to potentially drive the therapeutic algorithm across different BC stages [17–19]. In particular, VI-RADS Score 1 and 2 have been demonstrated to predict non-invasive disease at Re-TURBT [20]. Therefore, in the CUT-*less* trial, VI-RADS utilisation represents the ideal and currently most validated intervention to safely cover the primary TURBT pitfalls related to the risk for BC understaging.

On the other hand, the use of White-Light (WL) alone during TURBT procedures may miss lesions that are present but not visible. As such, the use of enhanced cystoscopy technologies is recommended when available and PDD is used as an adjunct to WL cystoscopy by preoperatively instilling hexaminolevulinate into the bladder. Importantly, a large body of evidence has demonstrated that fluorescence-guided resections are significantly more sensitive than conventional WL procedures for the detection of malignant bladder lesions, particularly CIS. Consequently, PDD enables to achieve more complete resection, to improve TURBT quality indicators, and consequently to have a positive impact on both recurrence and progression outcomes [21–24]. Therefore, in the CUT-*less* trial, the implementation of PDD-TURBT is intended to cover the pitfalls related to the risk of persistent NMIBC after the primary resection.

Main goal of our trial will be to demonstrate non-inferiority between our novel multidisciplinary approach and the current EAU NMIBC surgical pathway. This evidence may contribute to re-evaluate the necessity of second resections in selected cases thus potentially improving the NMIBC patient's perspective while limiting the social and economic burden of NMIBC management across national health systems.

Study Design and Hypothesis for Non-Inferiority

CUT-*less* trial is a single-centre, non-inferiority, phase IV, open-label, randomised controlled trial (RCT) with patients allocated in a 1:1 ratio to one of two arms. All the enrolled patients that already have been assessed with a preoperative mpMRI of the bladder and VI-RADS score determination, will either undergo standard of care (SoC) comprising primary WL TURBT followed by WL Re-TURBT within 2–6 weeks from initial WL TURBT or will undergo, primary PDD-TURBT, not followed by Re-TURBT. Additionally, both groups will receive standard care, including perioperative and/or adjuvant intravesical therapy as indicated by EAU Guidelines and surveillance according to risk-adjusted schedules.

Our hypothesis is that patients in the Experimental arm who will not undergo Re-TURBT will not differ from patients treated with the current SoC, with respect to early BC recurrences. Due to the putative advantages of combining preoperative mpMRI/VI-RADS and PDD resections, the primary outcome of early BC recurrences in each arm will be compared using a non-inferiority hypothesis. Accordingly, even if a similar number of events will be identified between the experimental and standard EAU algorithm, these advantages could support, in selected cases, omitting Re-TURBT instead of routinely and a priori performing it. The CUT-*less* trial schema is represented in Fig. 1.

Endpoints

Overall Aim

We seek to explore the impact of preoperative mpMRI and TURBT optical imaging enhancement by PDD-guided primary resection to improve the therapeutic algorithm and personalisation of NMIBCs.

Primary Endpoint

In a homogeneous cohort of mpMRI/VI-RADS selected patients, we will determine the proportion of early BC recurrences (i.e., within 4.5 months follow-up) in those patients with NMIBC treated by SoC (i.e., WL TURBT followed by WL Re-TURBT) compared to Experimental arm (i.e., primary PDD-TURBT omitting Re-TURBT).

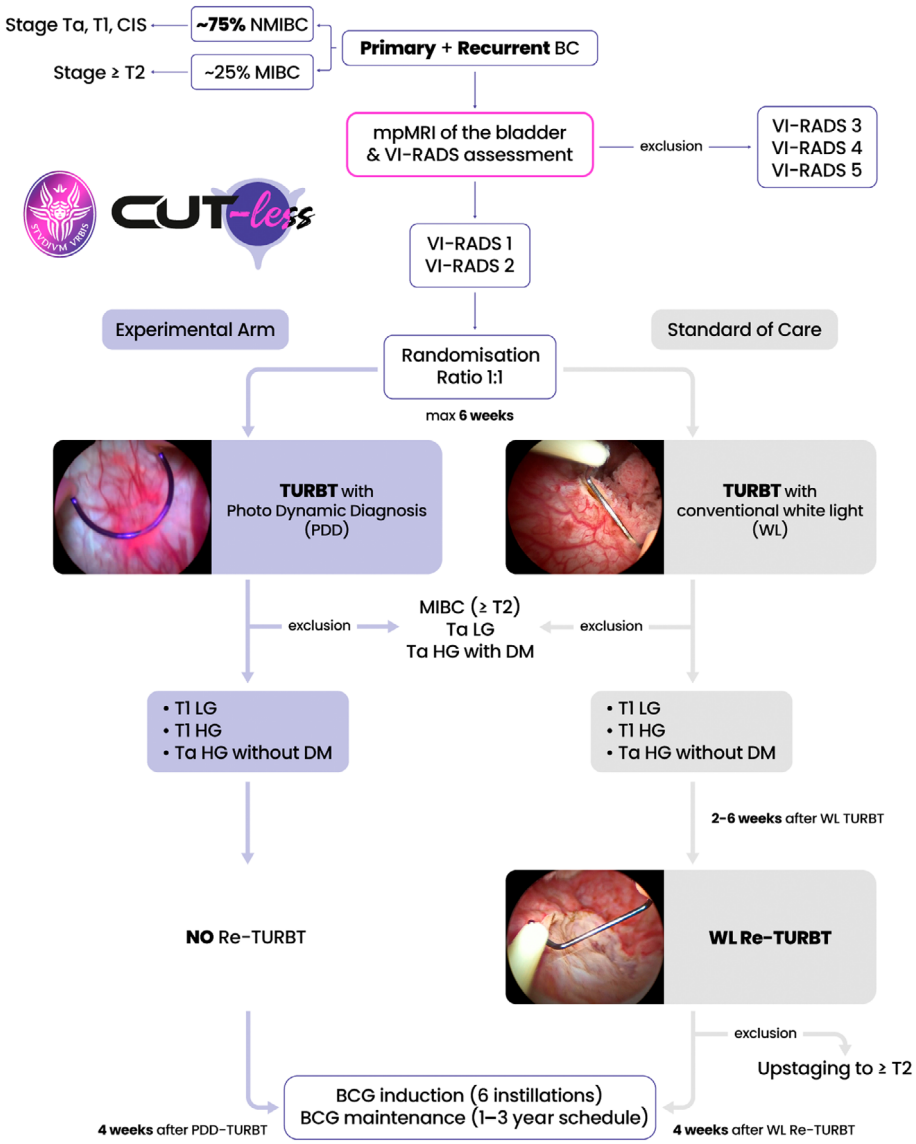
Secondary Endpoints

- To determine the proportion of late BC recurrences (i.e., after 4.5 months follow-up) in patients with NMIBC treated by SoC compared to our novel algorithm proposal.
- To determine the proportion of patients that progress from NMIBC to MIBC in patients treated with SoC compared to our novel algorithm proposal.
- To determine changes in health-related QoL (HRQoL) resulting from the physical and psychological benefit along with any harms associated with each strategy and with subsequent additional interventions. We will use generic QoL for cost-effectiveness analysis (i.e., EuroQoL five Dimensions five Levels [EQ-5D-5L]) and specific validated questionnaires to assess the outcomes of interest in the NMIBC population (i.e., European Organisation for Research and Treatment of Cancer quality of life questionnaire-30-item core [EORTC-QLQ-C30] and EORTC QLQ-24-item NMIBC [NMIBC24]).
- To perform a within-trial cost–benefit analysis to calculate incremental cost per Re-TURBT avoided and the cost-utility of the Experimental arm approach as measured by the incremental cost per quality-adjusted life year (QALY) gained at 2 years and over the patients' lifetime. A sub-analysis regarding specific total hospital costs and social health costs (e.g., productivity cost, informal cost) will be compared between the two arms of treatment.

Eligibility Criteria

This is a single-centre RCT sponsored by 'Sapienza' University of Rome, Department of Maternal Infant and Urologic Sciences. Preoperative mpMRI examinations and VI-RADS score assessment, as per inclusion criteria, will be a prerequisite for further enrolment in each patient. All the mpMRI examinations will be centrally performed and reviewed by the Department of Radiological, Oncological and

Fig. 1 The CUT-*less* trial schema. DM, Detrusor Muscle.



Anatomy-Pathological Sciences, 'Sapienza' University of Rome, Policlinico Umberto I Hospital. Patients will be considered eligible for registration into this study if they fulfil all of the inclusion criteria and none of the exclusion criteria, as listed in Table 1.

Methods

Description of the Trial Health-Related Requisite and Interventions

The CUT-*less* trial will be conducted according to the approved protocol and its amendments supplied by the Trial Sponsor (i.e., 'Sapienza' University of Rome, Department of Maternal Infant and Urologic Sciences) in accordance with the Principles of Good Clinical Practice (GCP) and following the health and social care recommendations provided by the European Medical Agency (EMA) and Clinical Trial Information System (CTIS) Guidelines in line with the Ethical Principles enounced in the latest version of the Declaration of Helsinki.

Any detailed description of the interventions are available from the EMA–CTIS (https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-507307-64-00) and ClinicalTrial.gov (https://clinicaltrials.gov/study/NCT05962541).

Pre-Requisite for Study Enrolment: mpMRI and VI-RADS Scoring Criteria

Preoperative mpMRI of the bladder with concomitant VI-RADS determination will be mandatory for all patients.

Table 1 Inclusion and exclusion criteria of the CUT-*less* trial.

Inclusion criteria
1. Female and male patients aged ≥18 years referred for clinical suspicion of primary or recurrent BC who have been advised to undergo TURBT
2. Patients with a TUR-confirmed diagnosis of NMIBC and candidate for second-look and resection (Re-TURBT) according to EAU Guidelines
3. No imaging evidence (i.e., mpMRI/VI-RADS Score 1 or 2) of muscle-invasive, locally advanced, or metastatic BC (i.e., only confirmed CIS, Ta, T1, N0, M0 will be considered eligible)
4. Patients who did or did not previously receive adjuvant intravesical BCG immunotherapy (i.e., BCG non-naïve or naïve patients) for previous BC history
5. Fit to undergo all procedures listed in protocol
6. Able to provide written informed consent
Exclusion criteria
1. Contraindication to TURBT and/or Re-TURBT
2. Initial TURBT diagnosis of MIBC (i.e., T2) or locally advanced BC (i.e., T3–T4)
3. Preoperative evidence of metastatic disease (i.e., cN1–N3 and/or cM1)
4. Visual evidence of low-risk NMIBC (solitary tumour and/or <1 cm) before initial TURBT
5. Visual evidence of MIBC on preliminary cystoscopy (i.e., non-papillary or sessile mass attached directly by its base without a stalk) or on pre-TURBT mpMRI/VI-RADS (Score 3–5)
6. TURBT diagnosis of NMIBCs not eligible for Re-TURBT according to EAU Guidelines (i.e., Ta-LG; Ta-HG with detrusor muscle in the specimen; primary CIS) [11]
7. Concomitant upper tract (kidney or ureteric) tumours on imaging
8. Contraindication to adjuvant intravesical BCG immunotherapy
9. Pregnancy and breast-feeding women
10. Unfit to undergo any procedures listed in protocol

The MRI protocol and VI-RADS Guidelines will rely on the original VI-RADS scoring algorithm previously published [14]. A genitourinary radiologist at our Institution (V.P.) with >20 years of experience, will be asked to assess each bladder lesion identified via mpMRI and to independently determine the VI-RADS score (from Score 1 to Score 5) on a per-lesion basis. The lesion which will be categorised as the one with the highest VI-RADS score will be labelled as the 'index' lesion. Only patients being categorised as VI-RADS Score 1 and/or Score 2 will be considered eligible in the CUT-*less* trial.

The SoC arm:

Initial WL TURBT The TURBTs will be performed by an experienced senior urologist. All TURBT procedures will follow the surgical recommendation listed in the EAU Guidelines [11]. These patients will undergo standard WL TURBT (wavelength 400–800 nm) using novel endoscopic equipment with light-emitting diode (LED) technology, full high-definition (FHD) resolution and using bipolar energy for resection. Each resected bladder lesion will be numbered and separately sent for final histopathological evaluation using specific surgical checklist [25]. The tumour/s location will be annotated in the surgical checklist and a copy of it will be attached to the path-report request in order to map each tumour localisation. Histopathology evaluation of the TURBT specimens will be performed by dedicated uropathologists. Tumour stage will be assigned according to the American Joint Committee on Cancer TNM Staging System, while tumour grade will be determined according to the 1973/2004 WHO system. The presence of lympho-vascular invasion in the lamina propria, concomitant CIS, and histological subtypes will be also assessed.

WL Second-resection (Re-TURBT) Re-TURBT procedures should be performed within 2–6 weeks following initial surgery by the same surgeon who performed the initial TURBT. Re-TURBT procedures will have to sample the scar site/sites of the first resection. All Re-TURBT procedures will be carried out under WL (wavelength 400–800 nm using novel FHD technology) and using bipolar energy for resection. Any additional bladder lesion found during the procedure will be excised and sent for separate histopathological evaluation. Each specimen collected during Re-TURBT will be sent labelling the area of localisation in order to ensure the correspondence with the primary TURBT tumour site.

The Experimental Arm:

PDD-TURBT All eligible patients in the Experimental arm will have hexaminolevulinate (85 mg in 50 mL of PBS) instilled into the bladder by catheterisation. In the operating theatre, the bladder will be illuminated with blue light (wavelength 380–450 nm) using novel equipment with LED technology and FHD resolution in adjunct to WL. The surgeon will perform the resection according to the common 'chips' or '*en bloc*' resection strategy of the bladder lesions or suspected flat areas. At the end of the resection, once surgical haemostasis has been obtained, the resection bed of each bladder lesion will be again scoped with blue light as to check for the accurate tumour tissue eradication both on the resection bed and at the level of the surgical margins and surrounding areas.

Adjuvant BCG

All patients will undergo adjuvant intravesical immunotherapy protocol with BCG in accordance with the EAU Guidelines recommendation. The adjuvant BCG immunotherapy protocol will be started 2 to 3 weeks after initial TURBT or Re-TURBT. The induction course will consist of one instillation every week for 6 consecutive weeks, followed by at least 1 year of maintenance instillation with 3 weekly instillations every 3 months for the first two schedules and then every 6 months [11]. The designated BCG strain will be BCG-RIVM (Medac GmbH).

Sample Size Calculation

The cohort of interest will be represented by intermediate-/high-risk NMIBCs who are currently those eligible for Re-TURBT according to EAU Guidelines [11]. For the primary outcome of the proportion of early BC recurrence a literature-based incidence estimates of 10% was applied [26,27]. A margin of 10% clinical unimportance was applied, representing the acceptable risk of disease understaging for the event of early BC recurrence in a population already screened by mpMRI and VI-RADS score.

Based on these assumptions and using 80% power and a 2.5% one-sided alpha, 142 patients per arm will be required to power the study for non-inferiority.

To achieve this, prior to randomisation, we will screen potential eligible participants by VI-RADS score determination, and we will exclude patients suspected of MIBC (15–20%) and, from the remaining NMIBCs, exclude low-risk disease (25–30%). Furthermore, we predict 35–40% of these patients will be recruited based on willingness to participate or missed opportunities for recruitment. Thus, total subjects required in study would be 284 equally distributed within the Experimental (n = 142) and SoC arms (n = 142). However, given pre-computed risk of 15% withdrawal/loss during follow-up, the total number of patients that will need to be randomised will be 327 across the Experimental (n = 163) and SoC (n = 164) arms.

Randomisation and general analysis principles

Patients will be randomised to the intervention (Experimental) or control (SoC) arms in a 1:1 ratio, using an unstratified random permuted block approach. Randomisation will be determined remotely using a web-based algorithm provided by sealedenvelope.com, which will release a system-generated randomisation code to authorised investigators.

Analyses will follow a modified intention-to-treat principle: Randomised patients who are found at initial TURBT to have MIBC (T2) or low-risk NMIBC (Ta + low-grade [LG] tumours; Ta + high-grade [HG] tumours and detrusor muscle in histology specimen) will be excluded from further analysis. All other randomised patients with confirmed intermediate- or high-risk NMIBC (Ta, T1) and a recorded primary outcome within the defined time frame will be included in the analysis, regardless of whether the treatment they received was compliant with the protocol.

Statistical analysis will be carried out using R (R Foundation for Statistical Computing, Vienna, Austria) and MedCalc version 22 (MedCalc Software, Ostend, Belgium). Health economic modelling will be carried out using TreeAge Pro 2023 (TreeAge Software, Williamstown, MA, USA).

Analysis of the Primary Endpoint

The primary endpoint—early BC recurrence, defined as a histologically confirmed recurrence of NMIBC or progression to more advanced disease within 3 months of primary PDD TURBT or WL Re-TURBT—will be analysed using both unadjusted and adjusted approaches.

The initial unadjusted analysis will be based on a crude comparison of early recurrence rates in the two treatment groups, yielding a risk ratio, which will be tested against the chi-squared distribution in order to assess achievement of the primary non-inferiority comparison.

A subsequent adjusted analysis will be carried out using a fixed-effect logistic regression model. The following pre-specified covariates will be included in the model as fixed explanatory variables: treatment group (Soc or Experimental pathway), age (years), gender (Male/Female/Other), tumour stage (Ta; T1), tumour grade (G1; G2; G3 and LG/HG), CIS (Yes/No), number of tumours (1, 2–7, ≥8) tumour size (<3 cm; ≥3 cm), VI-RADS score (1; 2), prior NMIBC treatment (Yes/No).

Interim Analysis

Although there is no prior expectation of a major difference between the two arms in terms of the primary outcome, it is conceivable that one treatment strategy may be associated with a significantly better outcome than the other. Provision has consequently been made for the execution of an interim analysis for the primary outcome after 4.5 months follow-up has been completed for the initial 100 patients recruited to the study, using a conditional probability analysis [28]. The use of this conditional probability approach has the advantages that it does not require comprehensive a priori planning of the timing of interim analyses and also that, by virtue of its highly conservative internal assumptions, it does not require adjustment of the α value for the primary analysis in order to retain statistical power.

Analysis of the Secondary Outcomes

Late Survival Outcomes

1. The relative proportions of patients with late BC recurrences, defined as first recurrence after 4.5 months (including progression to MIBC, distant metastases, and death from BC) in patients without an early recurrence detected at the time of assessment of the primary outcome.
2. The relative proportions of patients with progression to MIBC, defined as the time from randomisation to first increase to BC Stage ≥T2 or distant metastases.
3. Time to late BC recurrences, defined as for secondary outcome 1.

4. Time to progression to MIBC, defined as for secondary outcome 2.

Secondary outcomes 1 and 2 will be analysed using the same approach as defined for the primary outcome. Secondary outcomes 3 and 4 will be plotted using a Kaplan–Meier survival analysis. Hazard ratios and 95% confidence intervals will be estimated using a Cox proportional hazards approach, using the same set of baseline covariates as identified for the primary outcome. Statistical significance of any between-groups difference observed will be estimated using the log-rank test.

Analysis of HRQoL

Results of generic (EQ-5D-5L) and specific (EORTC-QLC-C30 and EORTC QLQ-NMIBC24) QoL questionnaires will be presented as descriptive statistics. Scores will be scaled and calibrated according to the validated methods for each questionnaire. Change in HRQoL metrics over time for a given group will be carried out using the Friedman test, while between-groups differences in scores at fixed time points will be compared using the Mann–Whitney *U*-test.

Analysis of Health Economics

Two health economic analyses will be carried out: a short-term cost benefit analysis of incremental cost per TURBT avoided within the 4.5-month primary study duration and a longer-term cost-utility analysis using 2-year clinical outcomes to drive a lifetime model. The short-term cost benefit analysis will use a simple decision tree structure to estimate overall costs and event rates. Cost data for this analysis will be derived from detailed health care resource utilisation data derived from a subset of study participants.

The long-term cost utility model will use a Markov health state transition model to estimate aggregated costs and QALYs over both 2-year and lifetime horizons. Five mutually exclusive health states will be specified to capture patients with stable disease, local recurrence, progression to MIBC, distant metastases, and death. Health state transition probabilities, costs and health state utilities will be derived in the first instance from in-study data collection. Beyond the 2-year follow-up period, transitions will be extrapolated from the study where possible, with extrapolation parameters being informed by the broader published literature. Where insufficient study data are available for a specific transition, cost or utility estimate, literature-derived estimates will be used. Parameter uncertainty in both models will be explored using both univariate deterministic and multivariate probabilistic sensitivity analyses in addition to pre-specified multivariate scenario analyses.

Discussion

BC is a high priority area for research into both clinical and cost-effective management and the findings from the CUT-*less* trial will be possibly relevant and important to patient needs over the next years across the EU and worldwide.

Transurethral resection of bladder tumour is the SoC both to diagnose and treat the vast majority of NMIBCs. Nonetheless, to overcome the intrinsic limitations of TURBT, to achieve the desired complete resection, and to correct potential staging errors, a second endoscopic procedure (i.e., Re-TURBT) is recommended by EAU Guidelines for most intermediate- and high-risk NMIBCs categories [11]. However, there is still no currently available strategy to select the ideal candidate for this second procedure.

Notably, from a patient perspective, there are often considerable anxieties about transurethral resection procedures, risk of recurrences, and progression requiring additional therapies with potential mortality and long-term morbidity. TURBTs in general, are associated with possible significant postoperative and long-term complications and morbidity ranging from 5.1% to 43.3% according to the different series [29,30]. Specifically, the potential for complications during Re-TURBT is not trivial and haemorrhage, the need for blood transfusion, or bladder perforation can negatively impact patient care and lead to delays in treatment, ultimately influencing survival. Any TUR itself is therefore associated with reduced QoL, including in both mental and physical health domains [31]. Substantial reductions in HRQoL are most likely to come from repeated hospitalisations, surgical complications, invasive adjuvant intravesical treatments, and radical or palliative treatments for progression. As consequence, a secondary resection performed 2–6 weeks from the primary resection represents an additional burden in an already arduous BC pathway. To our knowledge this surgical scenario has never been scrutinised in the framework of a RCT despite the lack of evidence to uniformly support Re-TURBT in every case. Moreover, both European and American series have reported that performing Re-TURBT did not impact long-term progression-free survival and that the tumour status at repeat TUR had only a marginal role in influencing long-term cancer-specific survival [32–34].

Additionally, NMIBC is one of the most expensive cancers to manage on a per patient basis because of its high prevalence, high recurrence rate, need for adjuvant treatments, and the requirement for long-term surveillance protocols [35]. Because of the protracted clinical course of early-stage disease, its prevalence relative to MIBC, and its procedure-oriented surveillance, the associated cumulative medical payments are generally more substantial than those for

advanced disease. The average per capita spending (in Euros [€]) for NMIBC has increased in the last two decades, from €7000 to €9000 [36]. These increasing costs are mainly attributable to the more frequent use of endoscopy (e.g., cystoscopy, TURBT, Re-TURBT) and the adjuvant intravesical therapies. TURBT accounts for a substantial portion of total bladder treatment costs ranging from €3000 to €6000 depending on whether patients are discharged following the procedure or admitted for inpatient care [37,38].

Given these urgent needs for optimising the NMIBC algorithm, the CUT-*less* trial will explore a novel multidisciplinary approach for minimising the burden of surgical exposure to patients and for re-sizing the costs to EU healthcare systems by re-defining the selection criteria for NMIBC candidates for Re-TURBT procedures.

To answer the aforementioned dilemmas, the CUT-*less* trial will attempt to address:

1. **Non-inferiority clinical efficacy**: the oncological non-inferiority of the novel approach will be measured by the receipt of early BC recurrences, which acts as a surrogate for both adequate primary TURBT diagnostic staging and the completeness of the resection. Adverse events and complications during the duration of the study will be also investigated to examine the safety profile of the two different pathways.
2. **Health-related QoL improvement**: this will be measured by incremental QALYs gained when comparing the Experimental arm approach with the SoC for raw differences between QALY estimates. We will be exploring if this approach would result in a significant non-inferior or superior profile across most of generic and specific QoL questionnaire domains, thus providing evidence for physical and psychological benefit within the Experimental arm.
3. **Cost-effectiveness revision**: this will be assessed by modelling the surgical algorithm for patients with NMIBCs who will be able to avoid a second hospitalisation and also avoid an additional surgical procedure. In addition, we will explore costs of the model and health state changes over a patient lifetime to estimate the incremental cost when Re-TURBT is avoided, costs to the national health systems, and incremental cost per QALY gained with the aim to achieve a significant social and economic benefit for the future EU health policy strategies within urological malignancies.

In conclusion, the currently available EAU Guidelines rely on conflicting and out of date evidence, which may not offer a contemporary viewpoint as to the role of Re-TURBT. Our updated protocol which utilises both mpMRI diagnostic imaging and PDD-guided resections will be closely examined in the CUT-*less* trial, with the goal of more personalised, socially and economically sustainable updated NMIBC therapeutic pathways for use in the EU.

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Disclosure of Interests

Tanja Hüsch declares personal fees by employment at Photocure, ASA. The remaining authors do not have any potential conflicts of interest to disclose.

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Correspondence: Francesco Del Giudice, Department of Maternal Infant and Urologic Sciences, 'Sapienza' University of Rome, Policlinico Umberto I Hospital, Viale del Policlinico 155, Rome 00161, Italy.
e-mail: francesco.delgiudice@uniroma1.it; fdelgiu@stanford.edu; francesco.delgiudice@gstt.nhs.uk

Abbreviations: BC, bladder cancer; c, clinical; CIS, carcinoma *in situ*; EAU, European Association of Urology; EORTC-QLQ (-C30) (-NMIBC24), European Organisation for Research and Treatment of Cancer quality of life questionnaire (-30-item core) (-24-item NMIBC); EQ-5D-5L, EuroQoL five Dimensions five Levels; EU, European Union; FHD, full high-definition (resolution); HG, high grade; LED, light-emitting diode; LG, low grade; MIBC, muscle-invasive BC; mpMRI, multiparametric MRI; NMIBC, non-MIBC; PDD, photodynamic diagnosis; QALY, quality-adjusted life year; (HR)QoL, (health-related) quality of life; RCT, randomised controlled trial; SoC, standard of care; (Re-)TURBT, (second-look and resection) transurethral resection of bladder tumour; VI-RADS, Vesical Imaging-Reporting and Data System; WL, white light.

