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Prospective bladder cancer infrastructure for experimental and observational research on bladder cancer: study protocol for the 'trials within cohorts' study ProBCI

Anke Richters ,[1,2] Richard P Meijer,[3] Niven Mehra,[4] Joost L Boormans,[5] Antoine G van der Heijden,[6] Michiel S van der Heijden,[7] Lambertus A Kiemeney,[2] Katja K Aben[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Anke Richters;
a.richters@iknl.nl

ABSTRACT

Introduction A better understanding of the molecular profile of bladder tumours, the identification of novel therapeutic targets, and introduction of new drugs and has renewed research interest in the field of bladder cancer. We describe the design and setup of a Dutch Prospective Bladder Cancer Infrastructure (ProBCI) as a means to stimulate and accelerate clinically meaningful experimental and observational research.

Methods and analysis ProBCI entails an open cohort of patients with bladder cancer in which the trials within cohorts (TwiCs) design can be embedded. Physicians in participating hospitals prospectively recruit invasive (≥T1) patients with bladder cancer on primary diagnosis for inclusion into the study. Extensive clinical data are collected and updated every 4 months, along with patient-reported outcomes and biomaterials. Informed consent includes participation in TwiCs studies and renewed contact for future studies. Consent for participation in questionnaires and molecular analyses that may yield incidental findings is optional.

Ethics and dissemination The Dutch ProBCI is a unique effort to construct a nation-wide cohort of patients with bladder cancer including clinical data, patient-reported outcomes and biomaterial, to facilitate observational and experimental research. Data and materials are available for other research groups on request through www.probci.nl. Ethics approval was obtained from METC Utrecht (reference: NL70207.041.19).

Trial registration number NCT04503577.

Strengths and limitations of this study

- First nation-wide trials within cohorts study for bladder cancer.
- Unique availability of combination of clinical data, biomaterials and patient-reported outcome measures for bladder cancer cohort.
- Data sharing and collaboration are encouraged.

INTRODUCTION

After decades of limited progress, the field of bladder cancer is currently in motion. New therapeutic options were recently introduced and there is a better understanding of the molecular profile of bladder tumours. Although these developments caused a wave of renewed research interest, they have yet to be translated into significant improvements for patients with bladder cancer.

Improved bladder cancer outcomes are imperative and long overdue, with survival having long been stable at dismal rates. Bladder cancer is among the top 10 most common malignancies with approximately 550 000 annual new cases worldwide.[1] Most patients (~70%) are diagnosed with non-muscle invasive bladder cancer (NMIBC: Ta, Tis, T1). NMIBC is characterised by high recurrence rates and the 5-year progression rates to muscle-invasive bladder cancer (MIBC) range from 7% among Ta tumours to 20% among high-grade T1 tumours.[2] Patients with MIBC have poor overall survival (approximate 5-year survival rates of 40%) despite almost half of these patients undergoing radical cystectomy. To improve the survival of patients with bladder cancer, earlier detection is required and more effective local control with improved (neo)adjuvant, surgical and bladder-sparing treatment. Additionally, new therapies for metastatic disease are needed.[3]

The therapeutic landscape for bladder cancer is changing due to a shifting emphasis towards multimodal and bladder-preserving therapies in MIBC and several new therapeutic options for metastatic bladder cancer (mBC). New therapies include several checkpoint inhibitors (CPIs) that have been approved

since 2017 for treatment in the metastatic setting, and targeted therapies such as fibroblast growth factor receptor (FGFR) inhibitors and enfortumab vedotin. CPIs have shown durable response in a proportion (~20%) of patients with mBC, but overall response rates remain modest.[4] The introduction of these drugs was followed by a huge increase in the number of trials assessing the efficacy of these therapies[5] in both the muscle invasive (eg, as neoadjuvant treatment) and non-muscle invasive settings. In addition, the efficacy of CPIs in conjunction with or sequentially after other treatments, including chemotherapy, radiotherapy and additional immunotherapeutic agents is currently being assessed in clinical trials.

Simultaneously, efforts are being undertaken to predict which patients are most likely to benefit from specific treatments through development of companion diagnostics,[6] as well as via assessing the predictive value of molecular characteristics of bladder tumours.[7 8] The various molecular subtypes that have recently been identified in urothelial cancer differ in underlying oncogenic mechanisms, infiltration by immune and stromal cells, and histological and clinical characteristics as well as prognosis. However, apart from programmed death ligand 1 expression which exerts a mix of predictive and prognostic value for CPIs, this research has not yet yielded other clinically applicable predictors for treatment response.

Importantly, preclinical molecular findings have to be translated into a clinical application and eventually improve patient outcome, but this is hampered by several issues. The plethora of trials being executed among a limited proportion of the patient population results in slow patient accrual.[9] In addition, considerable discrepancies in characteristics between patients enrolled in trials and patients in clinical practice are present, thereby limiting generalisability and potentially validity.[10–12]

In addition to randomised clinical trials, observational research is important to guide bladder cancer management. Approximately 85% of the evidence cited in the 2020 European Association of Urology (EAU)-guidelines on MIBC and mBC is based on non-randomised studies, of which approximately half is based on observational research.[13] Important observational research efforts focus on the identification of prognostic and predictive biomarkers. Experimental studies yield limited opportunities in that area, because biomarker analysis are often only performed in the experimental arm and performed analyses lack comparability between trials.[14] In contrast, observational studies on biomarkers dwindle because of the major efforts required for the execution of each individual study (eg, patient recruitment and data and material collection). Routine collection of biomaterials from unselected patient populations would accelerate these efforts and provide the necessary platform to validate findings.

Here we describe the Dutch Prospective Bladder Cancer Infrastructure (ProBCI) as a means to stimulate and accelerate clinical research, to ultimately improve patient outcomes. ProBCI aims to establish a cohort of patients with bladder cancer serving as an efficient starting point for observational research with readily available extensive clinical data reflecting daily clinical practice, patient-reported outcome measures (PROMs) and biomaterial. It will also serve as a source that enables a fast and less selected accrual of patients and historical or concurrent control groups for single arm intervention studies.

METHODS AND ANALYSIS

Study design

ProBCI constitutes an open cohort (figure 1), where newly diagnosed patients will be included continuously over time. In addition, the cohort serves as a basis to conduct interventional research according to the trials within cohort (TwiCs) design (also known as cohort multiple RCT, in short: cmRCT design).[12] Under this design, all patients undergo standard of care by default. On initiation of a randomised trial within the cohort, patients who meet the eligibility criteria can be (pre-)selected based on available clinical data and are subsequently randomised. Patients who are randomised to an experimental arm are contacted for the trial-specific informed consent, while

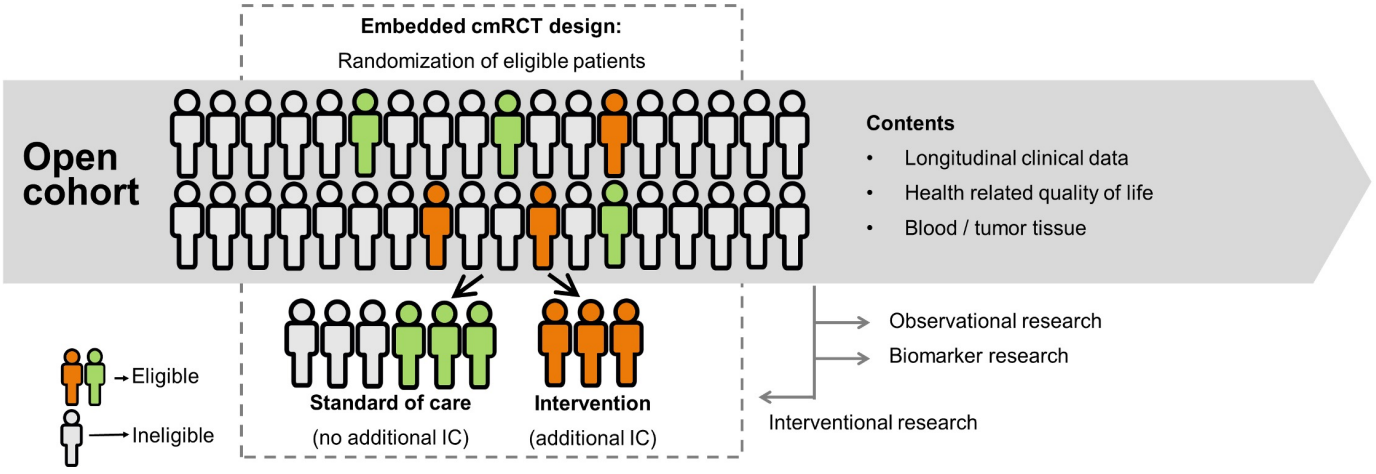

Figure 1 The cohort multiple RCT design. cmRCT, cohort multiple RCT = Twics; IC, informed consent.

those randomised to the control arm are not contacted and do not receive additional information.

Inclusion of patients and informed consent

All newly diagnosed patients of 18 years or older who provide written informed consent with high-risk non-muscle invasive bladder cancer (HR-NMIBC), MIBC and mBC, either urothelial or non-urothelial carcinoma, that is, all tumours of the bladder except pure Ta tumours, are eligible for inclusion in ProBCI by one of the participating hospitals. At the time of diagnosis or shortly thereafter, the patient is informed about the infrastructure. The information is provided by the treating physician (or research nurse/nurse specialist) after which the patient can decide about providing informed consent for the infrastructure. Informed consent for the ProBCI study covers the following aspects: (1) the linking and use of (clinical) data; (2) the overarching participation in the TwiCs design (broad consent[15]) including approval to serve as a control and approval to be contacted for future interventional research, either under the TwiCs design or otherwise; (3) longitudinal collection of liquid biopsiesand (4) use of residual tissue for research purposes. Two additional aspects of the informed consent are optional: (5) patients can provide consent for participation in questionnaires on health-related quality of life and (6) next-generation DNA and RNA sequencing that may yield incidental findings such as high-penetrance mutations for hereditary diseases. Included patients are entered in an online subject management system.

Data and biomaterial collection

The contents of the infrastructure include clinical data, PROMs and biomaterial. The Netherlands Comprehensive Cancer Organisation (IKNL) is an independent knowledge institute on oncological and palliative care in the Netherlands and provides a coordinating role in collection of data, PROMs and biomaterials based on the subject management system. Feasibility is achieved through central coordination that facilitates nation-wide identification of new patients with bladder cancer, clinical data collection within the Netherlands Cancer Registry (NCR) framework and collection of PROMs within the PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) registry (a collaboration of IKNL and Tilburg University), without additional efforts from hospitals or clinicians.

Clinical data

The NCR forms the backbone of clinical data and will be complemented with other data sources where necessary. The NCR is managed by the IKNL. Data are collected from medical hospital files by independent data managers of the NCR and do not require any additional effort from the clinicians or patients. The NCR transcends hospital boundaries, so patient data can be collected covering the entire disease course. Clinical data include patient and tumour characteristics, treatment information and follow-up including recurrence and progression data, and will be updated every 4 months. Annually, patients in the NCR are linked with the Municipal Administrative Database, in which death and emigration is recorded for all inhabitants of the Netherlands and patients' vital statuses are updated in the NCR. For specific research questions, clinical data collection may be extended retrospectively or prospectively to cover additional items and clinical data may be enriched with data from additional sources.

Patient-reported outcomes

Patients are sent questionnaires for collection of PROMs shortly after diagnosis and after 6, 12 and 24 months. Additional questionnaire time points may be added relative to specific treatments. The questionnaire includes demographic questions, questions regarding comorbidities, the EQ-5D-5L,[16 17] the EORTC QLQ-C30,[18] the QLQ-NMIBC24[19] and the QLQ-BLM30.[20] Patients can choose to receive questionnaires on paper or by electronic mail.

Biomaterials

Biomaterials collected in the infrastructure include blood and tumour tissue. Peripheral blood will be collected shortly after diagnosis at a routine venipuncture moment. Genomic DNA will be isolated from whole blood and cell-free DNA from cell-free plasma. Additionally, blood collection in university hospitals will be extended to specific time points in relation to treatments as well (table 1). These include single timepoint collection of cell-free plasma after radical cystectomy or bladder-preserving therapy and longitudinal collection of cell-free plasma before, during and after systemic therapy for cell-free DNA analysis.

Ethics and governance

The ProBCI infrastructure received approval of the medical ethical review committee of the University Medical Center Utrecht, The Netherlands METC Utrecht), in February 2020 (protocol number NL70207.041.19). All intervention studies to be conducted within the infrastructure (using the TwiCs design or otherwise) are required to obtain additional approval from a medical ethical review committee.

ProBCI is governed by the Foundation Prospective Bladder Cancer Infrastructure and a steering committee in which participating hospitals are represented. A sounding board provides input from the perspective of external experts, pharmaceutical companies and the bladder cancer patient association (*Leven met Blaas-of Nierkanker*). A scientific committee will review new research proposals based on scientific value.

Proceedings

Patient recruitment into ProBCI started in three academic hospitals (UMC Utrecht, Erasmus Medical Center, Radboud University Medical Center) in the Netherlands in October 2020. The expansion to other hospitals (both university medical centres and general hospitals) is ongoing and aims to ultimately cover the majority of

Table 1 Blood sample collection schedule by hospital type, patient subgroup and treatment

Subgroup	Treatment	Timing	Blood
All hospitals			
All patients	All treatments	► At diagnosis	► Roche cell-free plasma (for cfDNA) ► EDTA whole blood (for genomic DNA)
University medical centres			
MIBC/mBC	RC or BPT	► 4–6 weeks after treatment	► Roche cell-free plasma (for cfDNA)
MIBC/mBC	Neo-adjuvant chemotherapy	► Before initiation ► After two courses ► Before surgery	► Roche cell-free plasma (for cfDNA)
All patients	Checkpoint inhibitors	► Before initiation ► After two courses ► At first scan ► At progression	► Roche cell-free plasma (for cfDNA)

BPT, bladder-preserving therapy; cfDNA, cell free DNA; mBC, metastatic bladder cancer; MIBC, muscle-invasive bladder cancer; RC, radical cystectomy.

eligible patients. No end date or recruitment target is specified.

While coverage of prospectively included patients may be limited during the first year of ProBCI, longitudinal clinical data will already be available for all eligible patients in the Netherlands through the NCR. This will cover the approximately 3200 people diagnosed annually with HR-NMIBC or MIBC the Netherlands. Additionally, extensive clinical data are retrospectively collected for all the patients with primary metastatic bladder cancer diagnosed from 2016 to 2019, covering approximately 350 patients per year.

Data and material sharing

The ProBCI steering committee pursues its own research agenda, while also encouraging initiation of collaborations and initiatives by external groups that may be eligible to use the ProBCI infrastructure for research purposes. Requests for data/material will be reviewed by the ProBCI scientific committee for scientific rigour and merit and by other bodies where applicable. These may include the NCR's Supervisory Committee for compliance with NCR objectives and national privacy legislation and the Committee on Research with Human Subjects of the Radboud Biobank for legal and ethical aspects regarding biomaterials. More information on data requests, governance, research agenda and data and publication policy are available in online (www.probci.nl).

Patient and public involvement

The bladder cancer patient association (Leven met Blaas-of Nierkanker) was involved in the design phase of the study, including proof reading of the patient information material. As part of the ProBCI sounding board, they continue to provide additional input (eg, regarding research priorities, changes to the protocol) during the execution of the study. They also facilitate communication of the study's research findings to patients through their channels.

Ethics and dissemination

ProBCI is the first initiative to construct a nation-wide cohort of patients with bladder cancer including clinical data, PROMs and biomaterial to facilitate observational and experimental research. A similar initiative for colorectal cancer has provided the proof of feasibility of such a prospective cohort in the Netherlands.[21] The ProBCI infrastructure aims to facilitate a wide range of possible observational and experimental research. Table 2 shows examples of topics that could be addressed through the infrastructure and below we further discuss the added value of the infrastructure, including observational studies, biomarker studies and interventional studies embedded within the TwiCs design.

The timely availability of an extensive set of specific clinical data from a large patient population could prove valuable in addressing knowledge gaps in the treatment of patients with bladder cancer through observational studies. Such studies could range from descriptive studies on the bigger picture (eg, the median time to development of metastatic disease or long-term quality of life after bladder-preserving therapy) to predictive biomarker validation studies. Availability of biomaterial for a broad cohort of patients with bladder cancer undergoing various treatments with clinical outcomes could accelerate the identification and clinical validation of such biomarkers.[22]

In addition, observational research can carry out an important complementary role to RCTs. Comparative effectiveness studies in areas where trials have not (yet) been carried out may (temporarily) be the best available evidence yet and could be valuable if carried out timely and rigorously. Moreover, discrepancies often occur between clinical trial populations in which efficacy has been established, and the patient population in which interventions are applied.[23 24] Specifically, study populations in trials supporting authorisation of CPIs in other malignancies were considerably younger than patients

Table 2 Examples of research topics within Prospective Bladder Cancer Infrastructure

	Examples of research topics
Observational	
Descriptive	► The median time to development of metastatic disease in patients with primary and secondary muscle-invasive bladder cancer. ► The proportion of patients with metastatic bladder cancer treated with checkpoint inhibitors as first or second line therapy and survival outcomes.
Effectiveness	► Comparison of response rates and survival rates of patients treated with and without cisplatin-based chemotherapy in clinical practice to those in trial populations.
Biomarkers	► Predictive value of molecular subclass of muscle-invasive bladder cancer for response to neoadjuvant chemotherapy.
PROMs	► Quality of life of patients with muscle-invasive bladder cancer treated with radical cystectomy vs bladder-preserving therapy.
Interventional	
Single arm study	► Single-arm study of response rates to checkpoint inhibitors in patients with PD-L1 positive and negative metastatic bladder cancer. ► Comparison of response rates from single-arm study to concurrent controls from cohort with identical PD-L1 status.
TwiCs study	► Effectiveness of a protocol with liquid biopsies in combination with radiology compared with radiology alone for post-cystectomy monitoring of disease.

PD-L1, programmed death ligand 1; PROMs, patient reported outcome measures; TwiCs, trials within cohort.

in clinical practice.[25] Validation of findings from trials in patient populations reflecting daily practice is therefore important.

The TwiCs design embedded in the cohort asserts advantages for efficient conduct of trials. After the first description in 2010,[12] the TwiCs design has been successfully implemented in fields such as colorectal cancer, mental health and meniscus injuries.[21 26–28] The major advantage of this design is its approach regarding patient accrual. Compared with RCTs, cohorts can recruit a larger number and more representative sample of patients.[12] By using such cohorts as a source for trials, we expect to increase the recruitment efficiency, reach and representativeness of trial populations. This should uphold the feasibility of the multitude of anticipated RCTs among the patients with bladder cancer,[5] while providing a patient-centred approach to recruitment that is similar to routine healthcare.[12] It takes away the barrier for patients to consent to randomisation with the risk of not being offered the preferred treatment[29] and mitigates bias due to attrition and/or non-adherence.[30] These advantages are set off against a loss in flexibility regarding the control treatment, which is by default the standard of care. The TwiCs design has recently been implemented in a local cohort with patients with bladder cancer in London, UK, providing first indications of feasibility of this approach in the context of bladder cancer.[31]

To summarise, we have established the Dutch ProBCI to collect real-world prospective clinical data and provide a continuous bladder cancer cohort for clinical trials. With the research opportunities that ProBCI provides, we aim to increase and accelerate the availability of robust evidence to clinical practice, ultimately leading to improved outcomes of patients with bladder cancer.

Author affiliations
[1]Research and Development, The Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands
[2]Department for Health Evidence, Radboud Institute for Health Sciences, Nijmegen, The Netherlands
[3]Department of Urology, University Medical Center Utrecht, Utrecht, The Netherlands
[4]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands
[5]Cancer Institute - Department of Urology, Erasmus MC, Rotterdam, The Netherlands
[6]Urology, Radboud University Medical Center, Nijmegen, The Netherlands
[7]Department of Medical Oncology, Antoni van Leeuwenhoek Nederlands Kanker Instituut, Amsterdam, The Netherlands

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Competing interests NM reports grants and personal fees from Merck Sharp & Dohme, Roche, Janssen, AstraZeneca, grants from Sanofi and Pfizer, and personal fees from Astellas Pharma, Bristol-Myers Squibb, and Bayer outside the submitted work. JLB reports personal fees from Merck Sharp & Dohme, Roche and Janssen outside the submitted work. AGvdH reports personal fees from Merck Sharp & Dohme, Roche, Janssen, Sanofi, Ipsen Farmacuetica, Astellas Pharma and MML outside the submitted work. MSvdH reports grants and personal fees from Roche, Bristol-Myers Squibb and AstraZeneca, and personal fees from Merck Sharp & Dohme, Janssen, Astellas Pharma and Seattle Genetics outside the submitted work. AR, KKA, RPM and LAK have nothing to disclose.

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ORCID iD
Anke Richters http://orcid.org/0000-0002-1580-1543

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