



Reduce bladder cancer recurrence in patients treated for upper urinary tract urothelial carcinoma: The REBACARE-trial

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ABSTRACT

Background: Following radical nephro-ureterectomy for urothelial carcinoma of the upper urinary tract (UUT), the reported bladder recurrence rate of urothelial carcinoma is 22–47%. A single intravesical instillation of chemotherapy within 10 days following nephro-ureterectomy has the potential to decrease the risk of a bladder recurrence significantly. Despite recommendation by the European Association of Urology guideline to administer a single instillation postoperatively, the compliance rate is low because the risk of extravasation of chemotherapy.

Aim: To reduce the risk of bladder cancer recurrence by a single intravesical instillation of Mitomycin immediately (within 3 h) before radical nephro-ureterectomy or partial ureterectomy.

Methods: Adult patients (age ≥ 18 years) with a (suspicion of a) urothelial carcinoma of the UUT undergoing radical nephro-ureterectomy or partial ureterectomy will be eligible and will receive a single intravesical instillation of Mitomycin within 3 h before surgery. In total, 170 patients will be included in this prospective, observational study. Follow-up will be according to current guidelines.

Results: The primary endpoint is the bladder cancer recurrence rate up to two years after surgery. Secondary endpoints are: a) the compliance rate; b) oncological outcome; c) possible side-effects; d) the quality of life; e) the calculation of costs of a single neoadjuvant instillation with Mitomycin and f) molecular characterization of UUT tumors and intravesical recurrences.

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Conclusions: A single intravesical instillation of Mitomycin before radical nephro-ureterectomy or partial ureterectomy may reduce the risk of a bladder recurrence in patients treated for UUT urothelial carcinoma and will circumvent the disadvantages of current therapy.

Abbreviations		Ethische Toetsing Commissie (METC)	
CIS	Carcinoma in situ	MMC	Mitomycin
CT	Computer Tomography	RNU	Radical Nephro-Ureterectomy
CTCAE	Common Terminology Criteria for Adverse Events	TNM	Tumor Node Metastasis classification of Malignant Tumors
DNA	Deoxyribonucleic acid	UCB	Urothelial Carcinoma of the Bladder
IRB	Institutional Review Board	UUT	Upper Urinary Tract
METC	Institutional Review Board (IRB); in Dutch: Medisch	WHO	World Health Organization

1. Introduction

Urothelial carcinoma of the upper urinary tract (UUT) is a relatively rare disease with an incidence of 2 per 100.000 person/year in Europe [1]. At diagnosis 60% of UUT tumors are invasive versus only 15–25% for urothelial carcinoma of the bladder [2,3]. The outcome of UUT urothelial cancer is rather poor: the 5-year survival rate following radical nephro-ureterectomy (RNU) varies from less than 50% for pathological stage pT2 or pT3 disease versus less than 10% for pT4 disease [3]. The characteristics of high-risk UUT disease are: high-grade tumor at biopsy, multifocality, positive urinary cytology, transmural disease, hydro-nephrosis on imaging and a tumor size ≥ 1 cm [4–6]. For high-risk urothelial carcinoma of the UUT, RNU with excision of the ipsilateral bladder cuff is the treatment of choice, either by open or minimally invasive surgery [2].

Despite this radical surgical procedure, the bladder recurrence rate at two years following RNU for UUT urothelial carcinoma varies from 22 to 47% [4,7–9]. A recent study showed that 70% of these recurrences occurred in the first year following RNU [10]. Risk factors for a bladder recurrence following RNU are previous bladder cancer, tumor multiplicity, tumor location, tumor stage, and the operative modality [7,11]. For the prediction of intravesical recurrences following RNU, two studies designed predictive tools with an accuracy of 62%–69%. This indicates the difficulties in predicting which patients will develop subsequent bladder recurrences [11,12].

Recently, two randomized controlled trials have shown that a postoperative intravesical instillation of chemotherapy reduced the risk of a bladder recurrence following RNU [8,9]. A meta-analysis of these two studies showed that an intravesical instillation with chemotherapy within 10 days following RNU decreased the risk of bladder recurrence with 52%; the absolute risk reduction was 13% [10]. Despite the fact that the European Association of Urology (EAU) guideline recommends a single postoperative intravesical instillation with chemotherapy based on the result of these two studies [2], the compliance rate in clinical practice to this additional treatment is low. A survey among Dutch urologists showed that only 10% actually administers a postoperative instillation [10]. This reluctance is mainly due to the fact that a fresh wound is present in the bladder, which could lead to extravesical leakage of chemotherapy and with that potential life-threatening sequelae [13].

Here, we present the REBACARE study, in which patients receive a single intravesical instillation with chemotherapy just before RNU or partial ureterectomy for an UUT urothelial carcinoma. As subsequent bladder recurrences probably result from intraluminal seeding and the implantation of cancer cells [14,15], a preoperative instillation with chemotherapy could eradicate possible seeding of cancer cells in the

bladder. This neoadjuvant strategy has previously been shown to be effective in the treatment of non-muscle invasive bladder cancer using device-assisted instillations of Mitomycin [16]. The approach of a single instillation with chemotherapy before surgery has the following advantages: i) it will circumvent the possibility of extravesical leakage of chemotherapy; ii) it will spare the patient an invasive diagnostic procedure (cystogram); and iii) it could result in a better compliance of urologists.

2. Study design

2.1. Study management

The REBACARE study is designed as a multicenter, prospective, non-randomized cohort study in a clinical setting. Inclusion of patients will take place from September 2017 till December 2019. The estimated end of the study is December 2021, two years following RNU or partial ureterectomy of the last included patient. The follow-up will be in accordance with the ‘EAU guideline for the treatment of upper urinary tract urothelial carcinoma’ in which the surveillance regimen consists of cystoscopy, urinary cytology, and CT urography scans [2]. Only bladder recurrences (urothelial carcinoma) within two years following surgery will be counted for study purposes. In case a bladder recurrence is suspected, a diagnostic biopsy is warranted to histologically confirm a urothelial carcinoma of the bladder (Appendix A for the flow-chart of the trial).

The relapse rate in the study cohort will be compared with the relapse rate of a matched historical cohort. This historical cohort will consist of patients older than 18 years who underwent a RNU or partial ureterectomy for urothelial carcinoma of the UUT, performed between 2001 and 2015 in the participating centers, received no perioperative intravesical instillation of chemotherapy and who had no previous history of a urothelial carcinoma of the bladder.

2.2. Population

Adult patients (age ≥ 18 years) who undergo a RNU or partial ureterectomy (open or laparoscopic) for a primary urothelial carcinoma of the UUT will be eligible. These patients will be selected from participating centers in the Netherlands. Approximately 150 RNU's for urothelial carcinoma of the UUT were performed yearly in the Netherlands between 2006 and 2010.

No exact information is available for the total number of partial ureterectomy procedures performed in the Netherlands for UUT urothelial carcinoma. However, probably, these numbers are increasing due to the growing elderly population who are diagnosed with UUT but

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