



REGISTRY FOR TREATMENT OF UPPER URINARY TRACT TUMOURS

A Multi-Center, International Registry to evaluate the treatment of Upper Tract Urothelial Cancer: Incidence, Indications, Treatment types and Outcomes.

Protocol ID: Registry Upper Tract Urothelial Cancer

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A Multi-Center, International Registry to evaluate the treatment of Upper Tract Urothelial Cancer: Incidence, Indications, Treatment types and Outcomes.

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PROTOCOL SIGNATURE PAGE

Confidentiality Statement

I agree to perform this registry, to maintain the procedures required to carry it out and to abide by the terms of this protocol.

This registry protocol is the property of CROES and may not be used or published without their consent. The data from the patients included are property of CROES and may only be used following given consent by CROES council.

SPONSOR REPRESENTATIVE

Name:

Date:

Signature:

INVESTIGATOR (S)

Name:

Date:

Signature:

TABLE OF CONTENTS

1. INTRODUCTION.....	7
2. OBJECTIVES.....	7
2.1 Study design	7
2.2 Population	8
2.3 Inclusion criteria	8
2.4 Exclusion criteria	8
3. METHODS	8
3.1 Study parameters/endpoints.....	8
3.1.1 Main study parameter/endpoint	8
3.1.2 Other study parameters.....	8
3.2 Data collection.....	8
3.3 Study Duration	9
3.4 Description of data to be collected.....	9
4. STATISTICAL ANALYSIS	9
4.1 Primary study parameters	9
4.2 Other study parameters.....	9
4.3 Handling missing and spurious data.....	10
5. ETHICAL CONSIDERATIONS	10
5.1 Regulation statement	10
6. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION	10
6.1 The Steering Committee	10
6.2 Handling and storage of data and documents	10
6.3 Monitoring and Quality Assurance.....	11
6.4 Amendments	12
6.5 Public disclosure and publication policy.....	12

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

(e)CRF	(electronic) Case Report Form
CROES	Clinical Research Office of the Endourological Society
DMS	Data Management System
IRB	Institutional Review Board
PI	Principal Investigator
UTUC	Upper Tract Urothelial Cancer
UUT	Upper Urinary Tract

SUMMARY

Rationale: Upper urinary tract tumours are relatively uncommon tumours and many treatment options exist.

Objective: To evaluate the incidence, indications, survival and outcomes of patients presenting with UTUC, as well as describe the distribution of different treatment types used.

Study design: This is an international observational study in which data is recorded from consecutive patients who undergo treatment for UTUC.

Study population: The study population comprises consecutive patients who are presenting with primary UTUC.

Main study parameters/endpoints: Primary end point of the study is overall and cancer specific survival at one year after diagnosis with UTUC following different kinds of treatment. Follow up will be as long as five years.

1. INTRODUCTION

Although upper urinary tract (UUT) tumours are relatively uncommon within the group of urothelial tumours, the incidence rate is increasing. Studies performed in the Netherlands, Denmark and the USA showed an increased incidence rate - in the last century - of tumours within the UUT (Cauberg *et al.*, 2009). A significant number of reviews assessed the management and predictive factors of urothelial cancer (UC). Most important prognostic factors for survival and recurrence of upper tract urothelial cancer (UTUC) are tumour stage and grade, with less important factors being type of treatment and multifocality (Cauberg *et al.*, 2009). Lughezzani *et al* (2012) stress in their review the need for multi-institutional studies to provide stronger evidence for these prognostic factors and promote the use of these factors in the clinical setting. The Clinical Research Office of the Endourological Society (CROES) initiated this registry to gain more insights into this disease entity. The aim of this registry is to evaluate the incidence, indications and outcomes of patients presenting with UTUC in relation to the different treatment modalities used.

2. OBJECTIVES

Primary Objective:

The aim of this registry is to evaluate the incidence, indications and outcomes of patients presenting with UTUC in relation to the different treatment modalities used.

Secondary objective:

To assess the impact of imaging enhancement on recurrence rate of UTUC.

2.1 Study design

This is an observational international multi-center study in which data on consecutive patients with UUT tumours are collected. Centers from every continent may apply for participation in this registry. Data will be collected from consecutive patients over a five year period. Patients' data at baseline visit, at one year, three years and five years after inclusion in the registry will be recorded, as well as data on intra- and postoperative complications, recurrence and survival in the whole study period. Data from all participating centers will be collected through electronic case report forms (eCRFs), with use of an online Data Management System (DMS), which is located and maintained at the CROES Office. Members of the CROES Office will perform all analyses.

2.2 Population

The study population comprises those patients presenting with (a) (suspected) primary UUT tumour(s) and are planned to undergo either nephroureterectomy, ureteroscopic diagnostics and/or ureteroscopic treatment, percutaneous treatment or adjuvant treatment in the participating centers.

2.3 Inclusion criteria

Observational data from patients who meet the inclusion criteria below will be recorded:

- Is presenting with a suspected primary UTUC (any stage)
- Is scheduled for treatment of UUT tumour
- Has signed informed consent

2.4 Exclusion criteria

No specific exclusion criteria are defined.

3. METHODS

3.1 Study parameters/endpoints

3.1.1 Main study parameter/endpoint

- Incidence of UTUC, indications and outcomes (i.e. recurrence and survival) for patients presenting with primary UTUC
- Distribution of treatment types for UTUC
- Intra- and postoperative complications (including Clavien-Dindo classification)

3.1.2 Other study parameters

- Tumor progression, cytology, biopsies, value of diagnostic imaging
- Recurrence rate of UTUC stratified by imaging modality

3.2 Data collection

This registry will follow all consecutive patients during five years who present with primary urothelial cancer of the upper urinary tract in the participating centers. All sites will include patients who meet the inclusion criteria. Data from patients will be collected up to five years after inclusion. All data will be collected through an online DMS maintained by the CROES Office. Local sites will fill out the eCRFs in this DMS at the appropriate time

points. The CROES Office will send regular updates on the database and is responsible for sending reminders to principal investigators (PIs) for providing the follow up data.

3.3 Study Duration

Recruitment of patients will take five years. Since patients will be followed for 5 years, the total study duration is 10 years.

3.4 Description of data to be collected

Data collection will be divided into the following categories: Patient / tumour characteristics, assessment, treatment choice and intra-operative details, post-operative details and complications, and follow up. The following lists all categories and type of data to be gathered.

Patient characteristics: demographics, risk factors, comorbidities and previous malignancies.

Assessment: symptoms, imaging type, cytology, TNM staging.

Treatment choice and intra-operative details: date, use of endoscopy, type of scopes, type of imaging enhancement, biopsies, results, neo adjuvant treatment specifications and treatment type.

Intra-operative: date, duration, antibiotics, type of treatment, results.

Post-operative: complications and Clavien-Dindo classification, instillation, adjuvant therapy, pathology.

Follow up: date, status (e.g. alive without cancer, alive with cancer), recurrence, diagnostics performed, cystoscopy, cytology, results.

4. STATISTICAL ANALYSIS

4.1 Primary study parameters

Primary study parameters are: incidence of primary UTUC, baseline characteristics of patients, treatment type including adjuvant treatment, recurrence at 1 year after recruitment, and survival status.

4.2 Other study parameters

Multivariate analyses will be performed to assess possible associations with geographical differences and risk factors for complications after surgery.

4.3 Handling missing and spurious data

All analyses will be carried out on available data, with reporting of proportions of missing data. All analyses will be performed using SPSS 20 or R 3.0 or higher. Results will be presented in tables reporting at least the number of subjects, mean, standard deviation, minimum and maximum for continuous data; and number of subjects and percentages for categorical data. For testing, a significance level of 5% will be maintained.

5. ETHICAL CONSIDERATIONS

5.1 Regulation statement

This study will be registered at the competent authority for observational studies. Since this is merely a registration study, no approval is needed from any Dutch Medical Ethical Committee.

6. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

6.1 The Steering Committee

The Steering Committee consists of one principal investigator from each participating country and has the overall responsibility of the study.

Tasks and responsibilities include:

- To create and approve the final protocol
- To co-author protocol amendments whenever necessary
- To select the network of investigators
- To monitor progress of study enrolment of centers
- To ensure a scientifically sound and safe conduct of the study
- To review and approve the statistical analysis plan
- To guarantee the integrity of data collection and analyses
- To address and resolve study management problems
- To assist in the analyses and presentation of the results

6.2 Handling and storage of data and documents

The investigator or his/her designee will document all data obtained during the study on the individual eCRFs provided by CROES. Investigators will have access to the DMS, and will receive their own username and password. Only data from their own center is accessible to investigators. Data managers from the CROES will have full access to all

data collected during this trial, for purposes of monitoring data collection and analyzing the data. The electronic database will be maintained at the central data collection site selected by the CROES council and shall be updated on a regular basis as determined by the CROES council. A manager, selected by the CROES council, at the central data collection site will maintain and coordinate the data collection. As determined by the CROES council, all PIs will receive feedback on the data collection regularly.

Patient data will be entered anonymous, the key to coded information is held at each study center for its own patients and is the responsibility of the local PI. All requested information must be entered into the eCRFs, and will be the responsibility of the local PI. Data entered into the DMS is fully encrypted and therefore anonymized for all participants. Handling of personal data is in compliance with the Dutch Personal Data Protection Act.

The number of centers participating in this study is unlimited, although all sites must receive approval of the CROES council before commencing the data collection in this registry. Prior to receiving approval of the CROES council, an IRB approval shall be provided to the central data collection center when mandatory according to local law. Subject to the approval of the CROES council, the PI at study sites should preferably be a member of the Endourological Society. Study sites may be proposed by the members from the Steering Committee or on recommendation from a third party.

Data management and data analysis shall be the responsibility of the Steering Committee. Representatives of the CROES council may join the meetings of the Steering Committee.

Primarily, data belongs to the CROES in its function as an organ of the Endourological Society. After a request to the Steering Committee and receiving authorization from the CROES council, study participant members can present data at relevant occasions.

6.3 Monitoring and Quality Assurance

Monitoring this registry will be done by data managers at the CROES office. All data entered into the web-based data management system will be secured and checked for irregularities. In addition, the DMS provides detailed overview reports of inclusion and runs queries to check for inconsistencies in collected data, to ensure a reliable dataset. To minimize missing data, regular messages will be sent to investigators to encourage and remind them of entering data collected at follow up time points.

During the registry or after the registry has been completed, the Steering Committee and/or CROES representatives may carry out an audit. The audit will focus on data source verification and critical values in the database. Regulatory bodies may also inspect the study. If a regulatory authority contact an investigator with a request for an inspection, the investigator must inform CROES immediately.

6.4 Amendments

Amendments are changes made to the research after a favourable opinion by the Steering Committee has been given.

6.5 Public disclosure and publication policy

The Steering Committee will revise and give final approval to any paper derived from the data collected in the course of the study. Based on contribution and level of input, the Steering Committee will determine the author names and order of those authors on any paper derived from this dataset.

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